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# ARCHIVES OF DISEASE IN CHILDHOOD

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## *Annotations*

# Cholesterol and diet

Of recent years it has become increasingly apparent that the blood cholesterol concentration of a population is closely related to the prevalence of ischaemic vascular disease in that population. Pioneering epidemiological work by Ansel Keys in Minnesota (the Seven Countries Study) was the first to show this clearly.[1] Over the succeeding quarter century others went on to show that what was true of populations was also true of individuals,[2 3] that it was the cholesterol in low density lipoprotein that was deleterious,[4] and that high concentrations of high density lipoprotein were protective.[5] Low density lipoprotein appears to be the major source of cholesterol in atheromatous lesions, and high density lipoprotein is important in removing cholesterol from the arterial wall and returning it to the liver. Recent investigations have shown that lowering the low density lipoprotein and raising the high density lipoprotein cholesterol concentrations in the blood of high risk individuals reduces their risk of heart disease (the Helsinki Heart Study).[5]

There is now good evidence that atherosclerosis begins early in life.[6–8] Not only are atheromatous plaques found in young adults killed accidentally or in war,[9] but fatty streaks can be found in the aortas of 3 year olds and in the coronary arteries in the second decade of life. Newman *et al,* in a carefully conducted community study in Bogalusa County, Louisiana, showed that of those young people (age 5–24) dying of accidents or non-vascular disease in early life, the vast majority had aortic fatty streaks or atheromatous coronary plaques.[6] These streaks or plaques correlated closely with previously measured cholesterol, low density lipoprotein, and very low density lipoprotein concentrations and also with blood pressure; there was an inverse correlation with cholesterol in high density lipoprotein. Blood lipids, therefore, are important even in children as risk factors for the development of atherosclerosis. The concentrations of blood lipids vary between populations and diet is a major (although by no means the sole) factor in determining the blood lipid concentrations.

As paediatricians we have two separate problems to consider:

(1) What advice do we give to improve the health of the community as a whole?
(2) What do we do about high risk individuals?

### (1) Community advice

PRESCHOOL CHILDREN

Considerable disquiet exists among paediatricians and nutritionists over the advisibility of altering the fat intake over the first few years of life. Fat is an important energy source to the infant and young child. Infants fed low fat milks grow less well,[10] and the larger quantities of protein and solutes these infants consequently take in carry the potential hazard of azotaemia and renal damage.[11] In addition there is a possible risk of deficiency of fat soluble vitamins.

Over the age of 1 year there is little evidence that a low fat intake per se does any harm as long as basal requirements of fat soluble vitamins and of essential fatty acids are maintained.[11] A reduction in fat content implies a less energy dense diet, however, and, often, one that is less palatable. When this is combined with the frequently recommended increase in dietary fibre, a diet is produced that is relatively unattractive to the toddler or young child, and poor growth[12 13] or actual failure to thrive may result.[14]

Nevertheless a reasonable middle course can be found. The fat intake of many British children currently exceeds 50% of total energy. This can be reduced to 35% without prejudicing their energy intake or producing an unpalatable or vitamin deficient diet. In addition, much of the saturated fat can be replaced by monopolyunsaturates or polyunsaturates, which will themselves lower the blood cholesterol concentration. As a 1% reduction in total plasma cholesterol is associated with an approximately 2% fall in mortality from coronary heart disease in a population,[15] even this modest recommendation is likely to have a significant effect on the long term health of our population.

THE ROLE OF DIETARY CHOLESTEROL

It has been traditional to recommend restriction of dietary cholesterol as well as limiting total and saturated fat intake both in normal people and in those with hypercholesterolaemia. Most cholesterol, however, is endogenously synthesised and recent research suggests that a low cholesterol intake may be less important than previously supposed. A group of adult volunteers including both normal subjects and those with hypercholesterolaemia,

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while eating an otherwise 'healthy' high fibre, low fat diet, did not alter their blood lipid concentrations when they increased their dietary intake of eggs (which are very rich in cholesterol) from two to seven per week for an eight week period.[16] More work needs to be done in this area but for most people total and saturated fat intake is likely to be more important than intake of dietary cholesterol. (There may, however, be a small group of people who are unduly sensitive to dietary cholesterol changes.)

## (2) High risk individuals

One in 500 children has familial hypercholesterolaemia, a dominantly inherited defect of the low density lipoprotein receptor gene that is associated with raised plasma cholesterol concentrated almost entirely within the low density lipoprotein fraction and a family history of premature vascular disease. In many cases heart disease will occur in early to middle adult life. One in a million will inherit homozygous hypercholesterolaemia, receiving a defective gene from each parent. These children have very high cholesterol concentrations (even exceeding 20 mmol/l), skin and tendon xanthomas, and develop vascular disease in late childhood or adolescence. Very few live through their 20s. They need heroic measures to treat their disease (combined heart and liver transplantation has been tried) and diet alone will have little effect. Most families with familial hypercholesterolaemia in our population still remain undetected. As there is every likelihood that the prognosis in children with this genetic disorder can be improved by improving their diet and lifestyle,[4 5 15] all children from families with a history of premature vascular disease should be screened and appropriate advice offered to those from affected families.

These patients deserve early and intensive management starting in childhood. Their prognosis for leading a healthy adult life is poor, and they may well be struck down prematurely at a time when their whole family is financially and emotionally dependent on them. They should be managed initially by diet alone, but if this is inadequate (as it may well be) there should be little hesitation in using effective modern lipid active drugs to reduce the plasma cholesterol fraction present in low density lipoprotein, and to raise that in high density lipoprotein.

Few would attempt to restrict dietary fat in infants and toddlers, even from high risk families, but sensible eating habits with a restriction of total fat to approximately 30–35% of total energy can be effectively managed by the age of 5 or even earlier with no evidence of deleterious effects on nutrition, growth, or social development, and with good long term compliance.[17 18]

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# nital glaucoma—a preventable cause dness

go two leading articles were written ged paediatricians to detect and refer congenital cataract within the first weeks of life.[1,2] These and other articles, r with an increasing awareness of the prob- y paediatricians, has led to a significant ecrease in the age at which treatment can be completed, so that it is within a critical but finite period of development. Congenital glaucoma is also important because it can be treated and because it is one of the major causes of preventable blindness in children. It too requires early treatment for a successful visual outcome but referral to appropriate centres is often late.

Congenital glaucoma is responsible for 4% of childhood blindness and in western Europe the incidence has been estimated at 1:12 500 live births.[3,4] The risk is higher if the parents are related, suggesting an autosomal recessive inheritance. If there is no consanguinity, however, the risk to future siblings of a single affected child is only 1:20 and it seems more likely that inheritance is multifactorial.[5]

Congenital glaucoma is due to a developmental abnormality of the trabecular meshwork so that aqueous humour fails to drain from the eye. In young children this causes enlargement of the eye (buphthalmos), raised intraocular pressure, corneal oedema, and optic nerve damage. More than half the cases are due to an isolated defect of the trabecular meshwork whereas others are the result of various forms of maldevelopment of the anterior chamber of the eye. Seventy per cent of cases are bilateral. A wide variety of systemic diseases are associated with an increased incidence of congenital glaucoma including neurofibromatosis, homocystinuria, Marfan's syndrome, Lowe's syndrome, Reiger's syndrome, and congenital rubella infection. A number of children with chromosomal disorders have been described with congenital glaucoma but none of the associations are strong enough to give a clue to the genetic basis of the disease.

The most severe cases present with a dramatic icture at birth or within the first few hours or days f life with opaque corneas, photophobia, and lepharospasm. When less severe, the signs are ore subtle, and the condition may not become parent for weeks or months. During this time raised intraocular pressure causes enlargement of the eye, corneal oedema, cupping of the optic disc, and the gradual development of visual field defects. When detected early, and when successful surgery is performed, optic disc cupping is reversible and the visual prognosis is good.[6,7] The outlook is worse the larger and more opaque the cornea.

Most children with congenital glaucoma present within the first six months of life and corneal clouding is the usual presenting symptom.[8] Buphthalmos, the 'ox eye' appearance so characteristic of congenital glaucoma, seldom itself worries parents as large eyes may be considered attractive. In severe or neglected cases the cornea becomes white but in the early stages all that may be noticed are hazy streaks which may have a very sudden onset. As the eye enlarges the cornea is stretched and Descemet's membrane splits and aqueous seeps into the cornea showing as linear streaks of corneal oedema that are visible to the naked eye. With oedema comes photophobia, blepharospasm, and watering.

In mild cases surgery by goniotomy is curative in 90% of cases with one or more operation. This procedure takes only a few minutes to perform and involves passing a blade through a small corneal incision and sweeping it around 180° of the anterior chamber angle. If the cornea is opaque, more complex surgery is required. Children with associated ocular developmental disorders and those requiring repeated surgery have a much poorer prognosis.

All children should ideally be screened for eye disease, not only in the nursery by a paediatrician, but again at 6 weeks, 8 months, 18 months, and 3 years.[9] At these ages screening may be by the health visitor, general practitioner, or paediatrician. Examination should include holding an ophthalmoscope 18" from the cornea to look for opacities in the media. The red reflex should be seen and if it cannot, there is some opacity: corneal, lenticular, or vitreoretinal. If the reflex is hazy or absent, a check should be made to see if the iris details are clear. If not, the problem resides in the cornea and could represent corneal oedema from congenital glaucoma.

Any asymmetry of the size of the eyes should be considered suspicious of congenital glaucoma, although a difference of 1 mm is within normal limits. Deciding whether the larger or smaller eye is abnormal can be difficult. Microphthalmos is commoner than buphthalmos and clues from the history such as photophobia and watering should be asked for. If in doubt, examination under anaesthetic with measurement of corneal diameters and intraocular pressure and fundoscopy may be necessary to make the diagnosis.

Photophobia sufficient to cause discomfort on a dull day or in artificial light is always a sinister symptom in childhood. If acute illnesses such as menigitis are excluded, ocular conditions such as injuries, albinism, retinoblastoma, corneal crystals, oedema, or dystrophies as well as congenital glaucoma should be considered as possible causes. Examination with a hand torch provokes a typical response with the child screwing up the eye and turning away as a tear falls onto the cheek.

Watering of the eyes without stickiness in infancy is unusual and merits careful consideration. Blockage of the nasolacrimal duct leads to a complaint of watering with stickiness. If the eye is not sticky a careful examination for other causes of tearing should be made so that the benign condition can be distinguished from the potentially blinding one.

The suspicion of glaucoma in a child should be treated with urgency if serious visual handicap be avoided.

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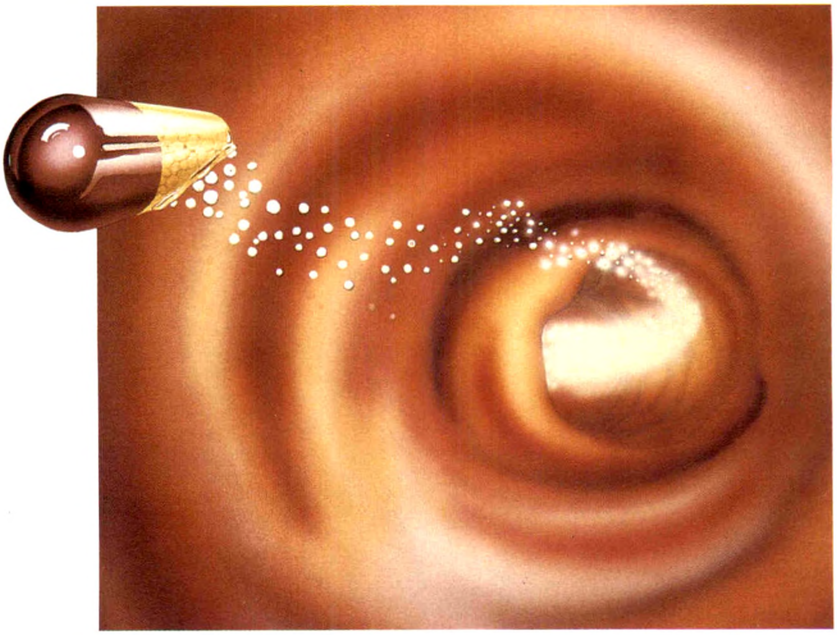

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## *Original articles*

# Controlled trial of standard pad and bell alarm against mini alarm for nocturnal enuresis

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SUMMARY Fifty six children aged from 6–16 years who wet their beds at night were entered into a controlled trial of two alarm devices: a traditional alarm using a wet sensor mat on the bed attached to an alarm bell out of reach of the child, and a mini alarm system incorporating a tiny perineal wet sensor attached to a small alarm worn on the child's clothing. A quota allocation system ensured comparability between the two treatment groups. The children were encouraged to use the alarm for four months. Both alarms were equally effective in helping children to become dry. There was no significant difference between the number of children unable to comply with treatment or to be helped by each alarm. The rate of acquisition of dryness was similar for the two groups. The traditional standard alarm was sturdier, more dependable, and easier to maintain, but the mini alarm had some advantages, particularly for girls. Both types of alarm are recommended for general use.

Enuresis alarms are popular and successful treatments for children who wet their beds. Most systems rely upon the original 'pad and bell' arrangement, in which a detector pad or mat is put beneath the sleeping child and connected to an alarm that rings as soon as the detector mat becomes wet.[1] Recently different systems have been developed in which a small wet sensor is placed near the child's perineum and is connected to a mini alarm attached to the child's clothing. When using the latter alarm the child does not have to get up out of bed in order to stop the bell ringing. There has been speculation that the smaller more convenient alarm might not be as effective as the standard alarm that forces the child to get out of bed to stop the alarm.

The aim of this study was to evaluate the relative merits of two different alarm systems and to assess the problems that the children, their parents, and their helpers experienced when using the alarms.

## Subjects and methods

The trial was conducted in healthy children aged from 6–16 years who had been referred to the enuresis clinic in the children's outpatient department of a large teaching hospital by general practitioners, clinical medical officers, consultant paediatricians, or urologists. The two doctors at the clinic were a consultant paediatrician who had extensive experience of managing enuresis and a clinical assistant/general practitioner who had no previous experience of treating enuresis, though she did have previous experience as a paediatric house officer.

The only children excluded from the trial were those with significant mental handicap (intelligence quotient less than 70), those with a serious systemic or psychiatric disorder, or those who had had a urinary tract infection during the previous two weeks. Fifty six children were enrolled in the trial. For each child bed wetting was a serious problem causing at least two wet nights weekly; most of them wet their beds five or more times a week.

At the initial visit a full history and physical examination was performed including examination of a fresh urine sample for infection or chemical abnormality. Specific enquiry was made about factors known to influence the outcome of treatment for enuresis.[2] These included: housing difficulties, family difficulties, or behavioural abnormalities assessed by scoring a Rutter A questionnaire.[3]

Throughout the trial the children were asked to keep written records (with the help of their parents) of wet and dry nights. A four week base line observation period was started. At the end of that time they were given an enuresis alarm—either a standard Eastleigh SM1 or a Mini Dri-Nite, according to a quota allocation system.[4] This allocation system enabled matching groups to be derived by allowing for sex, age groups (6–9 years and 10–16 years), Rutter A score (below 18 and 18 or above), and presence or absence of housing or family difficulties.

The child and accompanying parent were shown by the doctor how to use the alarm correctly, and instructed how to record wet and dry nights on a chart. It was emphasised that during the time that the alarm was used no other treatments such as drugs, 'lifting', or fluid restriction should be used.

The children were seen one week after the alarm had been issued and subsequently every two or three weeks according to response. At each visit the number of dry nights/week was recorded from the child's written record, as were any problems experienced with the alarm. All children were seen by one of the two doctors participating in the trial in order to provide consistency of advice and continuity of care.

Cure was defined as six consecutive weeks without a wet bed; at that point the alarm was removed. It was intended that the maximum period for using an alarm would be four months but extension to six months was permitted for children who were still showing some improvement after four months with the alarm.

At the end of the trial the two groups of patients were compared using the Statistical Package for the Social Sciences (SPSSX) mainframe computer program to assess the outcome of treatment in terms of numbers of dry nights achieved/week and the rate of achievement of dryness. Comparison of incidence of factors in the two groups was assessed by the $\chi^2$ test.

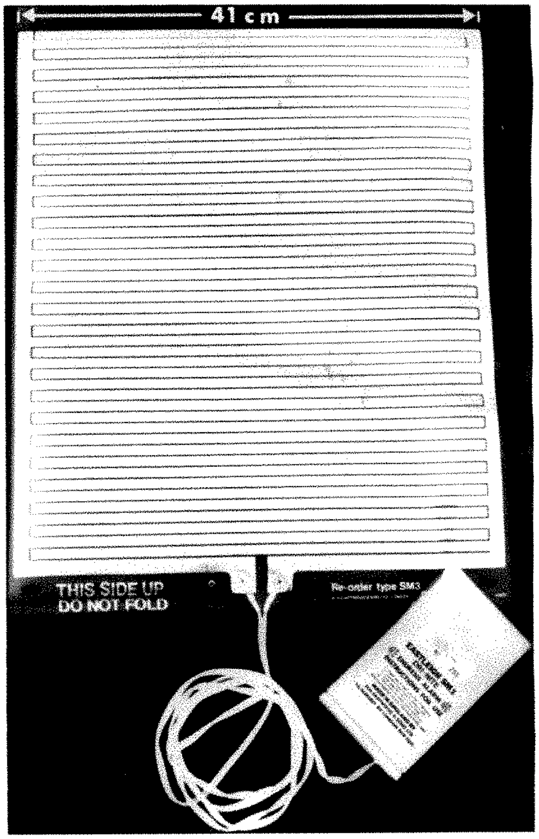

Fig 1 *The standard Eastleigh SM1 (pad and bell) alarm. The plastic mat contains a printed circuit connected by a lead to the alarm box, which is placed out of reach of the sleeping child.*

ENURESIS ALARMS

Two different Eastleigh* alarms were used, both of which are currently available. The standard SM1 alarm (fig 1) has a battery operated alarm box that is connected by a flexible lead to a single large plastic detector sheet (resembling a rear windscreen heater in a car). The detector sheet is placed on the child's bed on top of any protective mattress cover but under the bottom cotton sheet on which the child sleeps. The alarm is placed on a chair or cupboard near, but out of reach of, the child. The alarm is switched to the 'on' position at bed time. The child is advised to sleep naked from the waist down so that the first urine passed will reach the detector sheet speedily causing the alarm to sound. The alarm box also emits a flashing red light. The child is instructed to awaken fast, get out of bed, switch off the alarm, and go to the toilet to pass any remaining urine. The bed is then remade and the alarm reset.[5] The SM1 alarm requires a 9 volt battery, types PP3B, 6F22, MN1604, 6AM6, PP35 or 6LF22. The Mini Dri-Nite alarm (fig 2) consists of a much smaller battery driven alarm unit, a lead, and a tiny wet sensor. The sensor is placed inside a mini pant liner (for example, a 'carefree' panty shield, which is easy to peel apart from the waterproof backing and which accommodates the wet sensor easily). The pad is worn inside the underpants or knickers. The small alarm unit has a Velcro self adhesive cloth attachment that is attached to the front of the chest of the child's night clothes. The wet sensor in the pad responds to urine and triggers the alarm, which emits a high pitched sound. The child is advised to awaken fast and visit the toilet to void. Although the alarm noise can be cancelled by depressing a button on the side of the unit, the alarm sounds again when the button is released unless the sensor has been

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*Eastleigh alarms: N H Eastwood and Son Ltd, 7 Nursery Road, London N14 5QH.

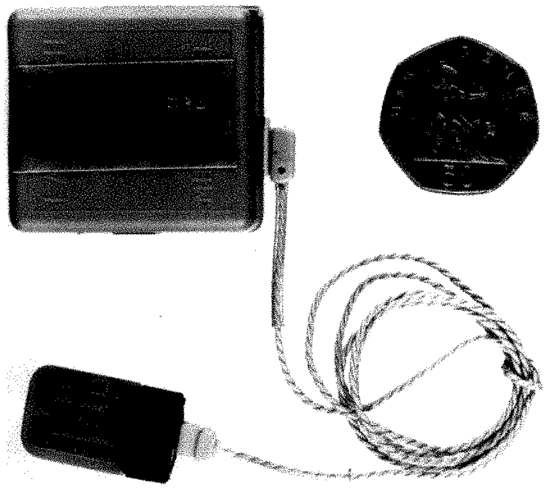

Fig 2 *Mini Dri-Nite alarm. The wet sensor disk, which is fitted into a panty pad, is connected by a lead to a tiny alarm box worn on the child's chest.*

carefully dried. The child and parents are therefore instructed to rinse the wet sensor in water and to dry it before replacing it in a clean panty shield. The Mini Dri-Nite is powered by a small 5,6 volt battery, type 7H34. The cost of the SM1 alarm (October 1988) was £37·00 plus VAT and postage, and that of the Mini Dri-Nite £32·00 plus VAT and postage. There is a 10% discount on orders of 100 or more. 'Carefree' panty shields cost 85p for 20 from many large stores and chemists.

## Results

Twenty seven children were allocated to use the SM1 alarm and 29 to use the Mini Dri-Nite (table 1). The quota allocation system permitted the even matching of the groups for most factors likely to affect outcome. Although seven children using the Mini Dri-Nite had behavioural abnormalities (as defined by Rutter scores of above 18) compared with only four using the SM1 alarm that difference was not significant. The two groups of children had almost identically severe bed wetting, and during the four weeks preliminary observation period had a mean of 5·2 wet nights/week.

To compare outcome, the number of dry nights/week for a two week period were counted at fixed intervals throughout the trial. The mean number of dry nights/week at these monthly intervals are shown for each group in fig 3. Those using the SM1 alarm who increased their number of dry nights/week from 1·7 to 6·2 had a similar rate of achievement of dryness to those who used the Mini Dri-Nite, who as a group increased their mean number of dry nights from 1·9 to 6·6. Within the trial period four children who had used the SM1 alarm and six who had used the Mini Dri-Nite had had six weeks completely dry. For those who achieved this 'total cure' the average time of 15 weeks for achievement of cure was similar for the two groups. Most of the families who dropped out of the trial did so during the first two months. As expected the 'drop outs' included an excess of families who had family problems, or children who had Rutter scores of above 18. The quota allocation system had ensured

Table 1 *Characteristics of children allocated to either standard or mini alarm. Figures are expressed as number (percentage)*

| | *Standard pad and bell alarm (n=27)* | *Mini alarm system (n=29)* |
|---|---|---|
| Sex: | | |
| Male | 18 (67) | 21 (72) |
| Female | 9 (33) | 8 (28) |
| Age (years): | | |
| 6–9 | 18 (67) | 19 (66) |
| 10–16 | 9 (33) | 10 (34) |
| Rutter score: | | |
| <18 | 23 (85) | 22 (76) |
| ≥18 | 4 (15) | 7 (24) |
| Family problems: | | |
| Yes | 8 (30) | 9 (31) |
| No | 19 (70) | 20 (69) |
| Housing problems: | | |
| Yes | 1 (4) | 0 |
| No | 26 (96) | 29 (100) |
| No of wet nights/week | 5·2 | 5·2 |

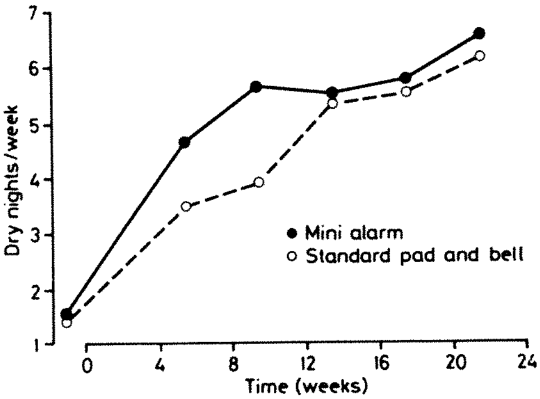

Fig 3 *The mean number of dry nights/week for the two groups using the mini alarm and the standard pad and bell. The alarms were issued at time zero.*

that these patients were equally distributed between the two groups, and of the 21 who had dropped out of the trial 10 came from the SM1 group and 11 from the Mini Dri-Nite group. There was no difference in the persistence (or lack of persistence) in using the respective alarms; the type of alarm did not affect the drop out rate.

The advantages and disadvantages of the alarms as reported by the parents and noted at the clinic are shown in table 2. The bulky SM1 alarm was robust, easy to maintain, and convenient (though at times embarrassing because of its size). False alarms were common, probably associated with the child sweating; the detector mats had a limited life and, for a third of the children, wore out within three weeks.

The Mini Dri-Nite was a small and convenient device that the child could easily take on holiday or to a friend's house without embarrassment. Despite its sensitivity, false alarms were rare; it did not require expensive replacement wet sensor mats. It was, however, not as robust, and frequently the system did not seem to be working. In some cases this was because the wet sensor fell out of the pant liner, in others the stream of urine seemed to miss the wet sensor, and until the manufacturers modified the alarm it was common for the leads to become detached from the alarm. The Velcro attachment for fixing the mini alarm to the child's nightwear was useless. Parents had difficulty in buying replacement batteries, which were not generally available.

## Discussion

The quota allocation system ensured that the two groups of children were satisfactorily matched for age, sex, severity of enuresis, behaviour problems, and housing and family difficulties. The doctor who provided most of their regular management was a clinical assistant who had received recent guidance on how to help children with enuresis but who did not have any preconceptions about the merits of the two different systems.

The final outcome for the two groups of children was similar. It is disappointing, and perhaps unusual, that a higher proportion of children entered in the trial did not become completely dry by four months. Factors militating against better results, however, were that this clinic attracts a large number of patients who are difficult to treat and children who have failed other courses of treatment from other health districts. Moreover, our definition of cure is unusually stringent, requiring the child to be completely dry for six consecutive weeks. It is noteworthy that even for those children who did not achieve 'cure', the number of dry nights increased steadily during the period that they used the alarm, and both children and their parents were well pleased with that improvement. For a child who

Table 2 *Advantages and disadvantages reported by users of standard alarm (n=27) and mini alarm (n=29)*

| | *Advantages* | *Disadvantages* | |
|---|---|---|---|
| **Standard pad and bell** | Comfortable to use | False alarms | (n=11) |
| | Batteries easy to replace | Detector mats wore out fast | (n=8) |
| | Alarm box robust: few breakdowns | Child switched alarm off and went back to bed | |
| | | Child has to be naked below waist | |
| | | Large device difficult to conceal | |
| **Mini alarm** | Small and unembarrassing | Alarm box Velcro fastening useless | (n=29) |
| | False alarms rare | Leads detachable from alarm | (n=7) |
| | Comfortable, particularly for girls | Sensor falls out of pant liners | (n=6) |
| | Sensitive | Expense of pant liners | |
| | Wet sensor is reusable and has long life | Batteries difficult to purchase | |
| | Less expensive | Boys' urine stream missed wet sensor | |
| | | Many inexplicable breakdowns | |

previously had only one or two dry beds a fortnight to have 11 or 12 dry beds a fortnight makes life a lot better.

For the purpose of this study we have assumed that those who failed to attend and dropped out of the trial are treatment failures because the experience is that, though a minority of those who fail to attend are subsequently found to have stopped wetting—and that is the reason for their non-attendance—most have dropped out because they find the alarm too awkward to use or lack family support, and are still wetting.[6 7] The number of 'drop outs' was considerable and—as is usually the case—they occurred early on. Thus by four weeks 23% had dropped out. For those who persisted with the alarm, both alarms were equally helpful.

Interestingly, there was no obvious difference in the results of treatments between the two alarm systems, given their different operating requirements. With the SM1 alarm placed out of reach, the child had to awaken thoroughly and get out of bed to stop the alarm ringing. With the mini alarm, although the children are advised to get up when the alarm sounds and to wash and dry the sensor, it is possible for the child, still in bed, to disconnect the alarm from ringing by pulling out the lead. Moreover, other forms of successful treatment of enuresis including 'dry bed training' seem to succeed because of the repetitive and demanding nature of the awkward tasks set for the child in the middle of the night.[8 9] It is as if the child becomes dry quicker if the regimen is more awkward. We had feared that the more convenient mini alarm might be less effective than the standard pad and bell alarm.

The acceptability of the different alarm systems to children, their parents, and those who are trying to help them is most important. As usual we found that the single factor that caused most trouble for the families was unreliability of the product. With all enuresis alarms there are serious problems for the users. The alarms are not as durable as one would wish and, particularly for a clinic that is regularly lending out alarms, durability is of great importance.[10] Inevitably there is always an element of misuse of equipment by children and their families. Detector mats need to be extremely strong and sturdy, for it is disappointing when they disintegrate too rapidly. The SM1 mat is better than most of the others that are on the market, but nevertheless for some children who wet their beds a great deal and who have sagging beds in which the mats get creased, the mat can wear out within three weeks. Leads that become disconnected easily are a worse problem. It is important for replacement batteries to be easily available. The tiny 5,6 volt battery (type 7H34) which powers the Mini Dri-Nite is not easy to obtain from general stores but is available from camera shops or with the help of hospital supplies departments. The SM1 alarm is powered by a larger 9 volt battery, which is available in several different makes all of which are compatible and easy to get.

Most standard pad and bell alarms, including the SM1 system, are associated with frequent false alarms as we found in this trial.[11] Apart from a crumpled mat a common reason for false alarms seems to be excess perspiration, and though one may advise the child to have less bedding and to open the bedroom windows, and the mother to put a thicker piece or a double folded piece of cotton material over the detector mat (or enclose it in a pillow case), false alarms continue to be a problem with most detector mats. False alarms are discouraging for everyone and the child feels cheated at being awoken when he is not wet. The relative absence of false alarms with the Mini Dri-Nite was therefore most welcome. It was difficult to be sure of the precise reasons for the frequent failure of the Mini Dri-Nite device. At times it was clear that the leads were becoming detached or that the alarm box itself was not working. At other times, however, we were not clear where the fault lay and merely issued another Mini Dri-Nite complete with wet sensor. A more reliable Mini Dri-Nite system would be welcome.

By the end of the trial we considered that the Mini Dri-Nite alarm was slightly more suitable for girls, firstly because its perineal sensor was not as acceptable to older boys and, secondly, because of the way that the boys' urine stream sometimes missed the wet sensor. For all children the compactness of the mini alarm was an advantage; they could hide it away in their bedroom when friends were with them. The wet sensor was sensitive and reliable but could be awkward to insert in a panty pad. We are aware of the enuresis alarm that is sold in the United States, and which relies on just two clips fixed to the pants of the child rather than to any specific sensor pad. If that is as reliable as a sensor pad it is likely to be more convenient.

One of the main problems with the Mini Dri-Nite is the inconvenience of the alarm attachment. There needs to be a secure, simple method by which the alarm can be clipped or pinned onto the child's pyjama jacket or T-shirt. The Velcro attachments did not hold the alarm effectively on the child's nightwear.

For any clinic regularly dealing with enuretic children it is worth becoming experienced in the use of more than one alarm, so that if an alarm does not suit a particular family a change in equipment can be made. We find that some children who do not get on well with the SM1 alarm fare much better with the mini alarm and vice versa, but our trial did not highlight any predictive factors. We believe that it is worthwhile for a clinic to have stocks of both types of alarm. It is probably unwise for clinics, other than the largest and the most specialised, to have more than two types of alarm because it is better for the staff to become really skilled and familiar with the equipment, and they cannot do that if there are many different types of alarm. Moreover, maintenance and provision of spare parts becomes awkward with too many different types of equipment.

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# Treatment centre size, entry to trials, and survival in acute lymphoblastic leukaemia

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SUMMARY In a population based series of 4070 children with acute lymphoblastic leukaemia treated in Britain during 1971–82, the five year survival rate improved from 37% for those treated in 1971–3 to 66% in 1980–2. During the same period there was an increase in the proportion of children included in the Medical Research Council trials and an increase in the proportion who were treated at centres with an average of at least six new patients per year. Survival rates were significantly higher for children who were included in the trials than for those who were not. Among children not in the trials, the survival rate was highest at centres treating at least six children per year and lowest at those with fewer than one per year. The increase in the numbers of children treated according to standardised protocols, particularly within controlled clinical trials, has had a major impact on the mortality from childhood acute lymphoblastic leukaemia.

In Britain during 1971–82, with a population of about 13 000 000 children below age 15, about 350 cases per year of acute lymphoblastic leukaemia were notified to the National Registry of Childhood Tumours maintained by the Childhood Cancer Research Group. Large numbers of these children with acute lymphoblastic leukaemia were included in the United Kingdom Acute Lymphoblastic Leukaemia (UKALL) trials, in which various combinations of chemotherapy and radiotherapy have been evaluated. Details of the protocols and results of these trials have been presented in a series of publications from the Medical Research Council Working Party on Leukaemia in Childhood.[1–8]

During 1971–82 most major treatment centres entered patients into most of the UKALL trials, and there has been a continuing process of concentration of treatment at such centres. For part of the period some centres used the trial regimens or similar ones, or carried out pilot studies of further modifications, without entering patients into the current trials. Hospitals other than specialist centres also adopted the improved forms of treatment without necessarily entering patients into the trials. By the end of the period under review, virtually all children with acute lymphoblastic leukaemia were treated according to standardised protocols.

Dramatic improvements in survival rates were achieved in the earliest of these trials, but little further improvement in rates of remission or survival was achieved among patients entered into the trials during 1972–9.[8] Trials conducted in the United States and Germany during the 1970s achieved higher success rates than the contemporaneous UKALL trials. As a result, the UKALL VIII protocol was introduced in 1980; this was based on a protocol developed by the United States Children's Cancer Study Group. The early results of this trial show considerable improvements on the preceding UKALL trials.[8]

In this paper we examine the trends in referral rates to specialist centres and in the proportions of children included in the trials, and the survival rates for children treated both inside and outside the trials and at centres of different sizes.

## Patients and methods

The Childhood Cancer Research Group has received copies of all notifications for children aged under 15 who had leukaemia diagnosed during 1971–82 and were reported to the national cancer registration schemes in England, Scotland, and Wales. During the same period, copies of all notifications for children entered in the Medical Research Council UKALL trials were also received. Additionally, from July 1977, copies of all notifications for the register of the United Kingdom Children's Cancer

Study Group (UKCCSG) have been sent to the Childhood Cancer Research Group. Confirmation of diagnosis and information on treatment and follow up were obtained from the hospitals at which the children were treated, from their family doctors or from the Medical Research Council Leukaemia Trials Office. Most of the deaths among these children are ascertained either through these records or through death certificates which are routinely sent to the Childhood Cancer Research Group for all children dying from malignant disease. Children not already known to have died have been flagged at the National Health Service Central Registers so that any deaths would automatically be notified to us, and have thus been followed up to the end of December 1986.

From all three sources of ascertainment combined, there were 4209 children with acute lymphoblastic leukaemia or acute unspecified or undifferentiated leukaemia who were domiciled in Great Britain at the time of diagnosis. Of these children 139 died before treatment could be started. The present analyses are based on the remaining 4070 children. For each child, the treatment centre was defined as the hospital from which the patient's chemotherapy was directed. Where a hospital closed during the period under review and treatment of childhood leukaemia was transferred to another hospital, or where treatment was administered by a team of clinicians working jointly at two hospitals, the treatment centre was taken to include both hospitals. The treatment centres were classified as follows according to the average number of patients in the series who were treated at them each year: A, average of at least six treated per year; B, average of at least one but fewer than six treated per year; and C, average of fewer than one treated per year.

The results have been analysed using standard methods to examine the effects on survival of inclusion in the trials and of type of treatment centre.[9]

## Results

Table 1 shows the numbers of children who were included in the Medical Research Council UKALL trials during the three year periods 1971–3, 1974–6, 1977–9, and 1980–2. The proportion of children included in the trials increased from 46% in 1971–3 to 64% in 1977–9. The proportion declined to 44% in 1980–2; this was largely because there was a gap of five months between the closure of UKALL VI and VII and the start of UKALL VIII, and because children at one very large centre were entered in a locally organised trial of maintenance treatment[10] or treated according to a pilot protocol for UKALL X. During 1977–82, some children with T cell acute lymphoblastic leukaemia at certain centres were included in a UKCCSG trial of treatment for T cell lymphoma and leukaemia.[11] The numbers of children treated at different categories of centre as defined in the methods section are also shown in table 1. The proportion treated at centres with an average of at least six patients per year increased from 52% of those diagnosed in 1971–3 to 65% in 1980–2 while the proportion treated at centres with fewer than one patient per year declined from 20% to 8%.

Table 1 *The numbers of children treated inside and outside the UKALL trials and at centres of various sizes during 1971–82*

| | *Year of first treatment* | | | | *Total 1971–82* |
|---|---|---|---|---|---|
| | *1971–3* | *1974–6* | *1977–9* | *1980–2* | |
| **In UKALL trials** | | | | | |
| Centre type:* | | | | | |
| A | 422 | 331 | 374 | 281 | 1408 |
| B | 59 | 208 | 199 | 107 | 573 |
| C | 16 | 55 | 59 | 26 | 156 |
| Total | 497 | 594 | 632 | 414 | 2137 |
| **Not in UKALL trials** | | | | | |
| Centre type:* | | | | | |
| A | 144 | 269 | 215 | 327 | 955 |
| B | 246 | 124 | 97 | 142 | 609 |
| C | 201 | 77 | 43 | 48 | 369 |
| Total | 591 | 470 | 355 | 517 | 1933 |
| **All patients** | | | | | |
| Centre type:* | | | | | |
| A | 566 | 600 | 589 | 608 | 2363 |
| B | 305 | 332 | 296 | 249 | 1182 |
| C | 217 | 132 | 102 | 74 | 525 |
| Total | 1088 | 1064 | 987 | 931 | 4070 |

*Definition of type of centre: A, average of at least six patients treated per year; B, average of at least one and fewer than six patients treated per year; and C, average of fewer than one patient treated per year.

The figure shows the overall difference in survival for patients included and not included in the trials. The proportions of the two sexes and values of the white cell count, factors known to be of prognostic importance, were similar for the two groups of children. In the 0–1 year age group, which has a poor prognosis, there was a smaller proportion of trial patients. When age was allowed for in the analysis, there was still a highly significant difference in survival rates in favour of the trial group ($\chi^2=102\cdot5$ on 1 df, stratified by period of diagnosis).

The survival rate was best for centres treating the

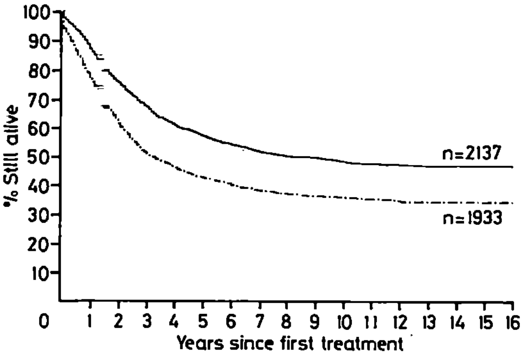

Figure *Actuarial survival curves for children with acute lymphoblastic leukaemia treated 1971–82: children included (—) and not included (— · — ·) in Medical Research Council trials. Log rank test for difference in survival rates, stratified by period of diagnosis and allowing for age: p<0·0001.*

Table 2 *Five year actuarial survival rates (%) for children treated inside and outside the UKALL trials and at centres of various sizes during 1971–82*

| | *Year of first treatment* | | | |
|---|---|---|---|---|
| | *1971–3* | *1974–6* | *1977–9* | *1980–2* |
| **In UKALL trials** | | | | |
| Centre type:* | | | | |
| A | 51 | 52 | 58 | 75 |
| B | 53 | 50 | 60 | 71 |
| C | 44 | 53 | 61 | 73 |
| All centres | 51 | 51 | 59 | 74 |
| **Not in UKALL trials** | | | | |
| Centre type:* | | | | |
| A | 30 | 49 | 50 | 60 |
| B | 28 | 40 | 44 | 63 |
| C | 20 | 38 | 33 | 50 |
| All centres | 26 | 45 | 46 | 60 |
| **All patients** | | | | |
| Centre type:* | | | | |
| A | 46 | 50 | 55 | 67 |
| B | 33 | 46 | 55 | 66 |
| C | 22 | 44 | 49 | 58 |
| All centres | 37 | 48 | 55 | 66 |

*Definition of type of centre: A, average of at least six patients treated per year; B, average of at least one and fewer than six patients treated per year; and C, average of fewer than one patient treated per year.

largest number of patients. The treatment centre groups were similar with respect to the sex ratio and the proportions of patients in different ranges of white cell counts. Children aged 10–14, who have a worse prognosis, were less likely to have been treated at a group A centre and correspondingly more likely to be in group C, but when age was allowed for there was still a highly significant difference in survival rates in favour of larger centres ($\chi^2$ for trend=38·4 on 1 df, stratified by period).

Effects of inclusion in the trials and of treatment at different types of centre were next considered together: for children included in the trials there was no difference in survival rates between centres of different size; for those not included in the trials, however, there was a noticeable pattern of higher survival rates at larger centres (table 2).

Changes over time in the five year survival rates for children first treated during 1971–82 are examined in table 2 in relation to inclusion in the trials and to size of centre. Overall there was an appreciable trend in rates from 37% for 1971–3 to 66% for 1980–2. For children in the trials there was little change in survival rate during 1971–9, but for children not in the trials there was a substantial improvement. The rates for 1980–2 showed a considerable improvement on 1971–9 for both trial and non-trial patients. Nevertheless the non-trial survival rate for 1980–2 had only reached that achieved for children included in the trials during the previous three years although, as already remarked, a substantial proportion of children not in the trials were treated at major centres. The difference in survival between treatment centre groups for children not in the trials was observed throughout 1971–82. The improvement in survival for 1980–2 was observed for all types of centre.

The effects of inclusion in the trials and size of treatment centre were very noticeable during the few months immediately after diagnosis, and it might be argued that this reflects some selection bias; however, when patients who had died within three months of diagnosis were excluded from the analysis, the differences between trial and non-trial patients and between those at different categories of treatment centre were still highly significant.

Although the great majority of deaths from acute lymphoblastic leukaemia in children occur within five years of diagnosis, there is a substantial risk of death beyond this time. So far 248 deaths have been recorded among the 1835 children surviving at least five years up to the end of December 1986. The subsequent survival rate for those who survived five years did not differ as between trial and non-trial patients. This rate was, however, significantly higher for centres in group A than for groups B and C ($\chi^2$=6·34 on 1 df, stratified by age and calendar period of diagnosis).

Of the 248 patients who died after five years or more 189 (76%) had suffered a first relapse at less than five years from diagnosis; 26 (10%) had a first relapse later than five years (maximum nine years); seven (3%) were in first remission from acute lymphoblastic leukaemia at the time of death; no information on time to first relapse was available for the remaining 26 (10%).

As yet only 16 second primary tumours have been observed in the series; 13 of these 16 patients have died. There was no obvious association of the risk of developing a second primary tumour with whether children were included in the trials or with treatment centre size, but this result should be treated with caution because of the small number of second primary tumours as a proportion of the total series.

## Discussion

There is considerable interest in questions concerning the centralisation of treatment for childhood cancer and leukaemia. Over the past 20 years there has been a continuing trend towards such centralisation in the United Kingdom; some indication of this is given in table 2. There has been very little published evidence on the effects on the survival rate for childhood acute lymphoblastic leukaemia of such centralisation—that is, of treatment at specialist centres or within controlled clinical trials. In the mid 1960s, when survival was generally extremely poor, it was found that children treated at specialist centres were more likely to survive.[12] More recently, an analysis of over 300 children with acute lymphoblastic leukaemia from the population based Greater Delaware Valley Pediatric Tumor Registry in the United States showed significant advantages in survival for patients treated at specialist cancer centres and for those who were treated according to standardised protocols.[13] The results of the present analyses agree with these findings. In the early 1970s there were large differences in survival rates between centres treating many patients and those where only a few were treated. These differences diminished in more recent years. To some extent this may be explained by assuming that some of the less successful smaller centres gave up treating children with acute lymphoblastic leukaemia during this period. Also, of course, even the smallest centres which did continue to treat some of these children will have had a larger total number of patients by the 1980s.

In addition to the overall pattern of higher survival rates at treatment centres seeing larger numbers of patients, there was considerable variation in survival between individual major centres. Among the 12 centres in group A, there was no association between survival rates and size of centre, but the five year survival rates of these centres ranged from 45% to 70%. Some of this variation is probably explained by random differences in the proportions of children with good or poor prognostic features at individual centres. Nevertheless, detailed analysis of the rates achieved at one centre suggests that some of the variation may be due to differences in the application of apparently similar treatment protocols.[14]

Overall the survival rate at the group B centres was lower than for group A and higher than for group C, but within group B there was no difference in rates between those centres with one, two, three, or four patients per year.

The effects on the survival rate of inclusion in the trials and size of treatment centre both persisted beyond three months from diagnosis. This suggests that the differences in survival rates cannot be explained solely by patients more frequently failing to achieve remission outside the trials and at minor centres.

The risk of first relapse after the completion of treatment generally appears to be low,[12 15 16] although first relapses have been recorded as long as nine years after entering remission both in the present series and previously.[17] The Childhood Cancer Research Group registry does not hold details of the relapse free survival time of all children as this would require repeated active follow up of very large numbers of patients. The results presented here show no evidence that mortality rates among those surviving at least five years are different for trial and non-trial patients, though because of the appreciable differences during the first few years after diagnosis, those included in the trials had a substantially higher chance of becoming very long term survivors. The higher probability of survival for children treated at major centres appeared to persist even beyond the first five years after diagnosis.

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## Addendum

Since the above analyses were carried out, further cases of childhood acute lymphoblastic leukaemia have been ascertained by the Registry. Ascertainment is now virtually complete for 1980–4, and most survivors have been followed up to the end of August 1988. There is thus now a greatly increased amount of data relating to children treated during the period of entry to UKALL VIII, a trial which used more sustained treatment than its predecessors and produced a higher survival rate. We have therefore analysed the data relating to trial entry, treatment centre size, and survival for children diagnosed in these years.

During 1980–4 there were 1558 children treated for acute lymphoblastic leukaemia, of whom 51% were included in the Medical Research Council trials. The great majority (66%) were treated at group A centres, with 28% at group B, and only 5% at group C. The overall five year survival rate was 68%. Within the trials the five year survival rate was 72%, compared with 64% outside the trials, and the difference between the survival curves was highly significant ($\chi^2=10{\cdot}0$ on 1 df, $p<0{\cdot}001$, allowing for age at diagnosis). For trial and non-trial patients combined, the five year survival rates at centres in groups A and B were very similar, 69% and 68% respectively, but the rate in group C was only 53%. There was no association between the survival rate and the number of patients per year within group B. Within the trials the survival rate was very similar at centres in groups A (72%), B (71%), and C (68%). For non-trial patients, the rates were 64%, 66%, and 48% respectively. These results show the continuing importance of treatment according to standardised protocols, particularly within nationally organised trials, for the achievement of the best survival rates in childhood acute lymphoblastic leukaemia. Since the 1970s, the survival rates at centres treating between one and six new patients per year have become very similar to those obtained at the largest centres, but those for children treated at centres with fewer than one new patient per year and not included in the UKALL trials remained considerably poorer.

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# Immunological evaluation in the early diagnosis of prenatal or perinatal HIV infection

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SUMMARY A longitudinal evaluation was carried out of the clinical, infective, and immunological progress of 34 children (who were aged 6 to 68 months—mean 25 months at the time of writing) born to 31 mothers infected with human immunodeficiency virus (HIV), over a mean observation period of 13·4 months. Clinical symptoms, not always clearly related to HIV became apparent in 11 children, and preceding immune abnormalities were documented in two of them. In eight children culture for HIV was positive, and six of these were symptomatic. No cancers were diagnosed and none of the children died. Immune abnormalities including hypergammaglobulinaemia, IgG subclass deficiency, low serum IgA concentration, antibody deficiency, a decrease in the number of CD4+(T helper) cells, and defective cellular responses to antigens, were found in seven of the children in whom culture for HIV was positive; in two of four who had symptoms and in all four who were symptom free and in whom culture was negative for HIV but in whom HIV antibodies persisted and who were older than 15 months; and in three of nine who were symptom free and in whom culture was negative with loss of HIV antibodies.

We conclude that serological diagnosis alone may be misleading and that additional immunological assessment may help to identify affected children. Analysis of humoral and cellular responses to antigens used for vaccination such as tetanus toxoid by measurement of specific antibodies and skin testing are simple and helpful in clinical practice.

Infants born to mothers infected with human immunodeficiency virus (HIV) may acquire the virus in utero or perinatally.[1] In contrast with adults, in whom infection with HIV can be diagnosed simply by detection of antibodies or antigens specific for HIV, serological diagnosis in infants is more difficult because maternal antibodies specific for HIV cross the placenta. Furthermore, detection of specific IgM or IgA, or both, which could be of infant origin, may merely reflect the contact of the child with noninfectious HIV antigens crossing the placenta; it is also prone to technical problems.[2] In addition, the exact length of time for which maternal antibodies persist is not yet known. Thus definite diagnosis of HIV infection in infants without symptoms can, at least in the first 2 years of life, only be achieved by cumbersome techniques such as virus isolation from peripheral blood cells.

Early diagnosis of infected subjects, however, may be crucial for appropriate care and treatment. Because the number of infants born to mothers positive for HIV is increasing, and not all these infants will be entered in studies from medical centres with accurate technical facilities for isolation or hybridisation of the virus, more information about the clinical and immunological course in these infants is needed.

From the longitudinal study of HIV in children that was started at the University Children's Hospital of Zurich in June 1986, we have selected data about 34 infants born to mothers infected with HIV to delineate further the association between clinical symptoms and immunological findings on the one hand, and the laboratory diagnosis of HIV infection on the other. The cohort in this analysis comprises more than one third of the 107 registered infants at risk of vertical transmission of HIV infection in Switzerland.[3]

## Patients and methods

### SUBJECTS

Criteria for infants and children to be included into this study were maternal HIV seropositivity before or at delivery as well as former or continuing drug abuse by the mother if HIV serology was positive only after delivery. Maternal and perinatal history were recorded following a questionnaire by review of the charts.

### PHYSICAL EXAMINATION

The children were seen at the outpatient clinic at three monthly intervals for clinical, immunological, and virological examination. A history was taken on each occasion and on physical examination special attention was paid to dystrophy, lymphadenopathy, hepatosplenomegaly, mucocutaneous infections, confirmed bacterial or viral infections, and persistent or recurrent diarrhoea or cough. To detect early signs that the central nervous system had been affected by HIV, by other neurotropic viruses such as cytomegalovirus, or by opportunistic agents, a detailed neurodevelopmental evaluation was carried out (depending on age) with the Bayley scales of infant development, a standardised neurological assessment adapted from Prechtl,[4] and the Stanford-Binet test.[5]

### IMMUNOLOGICAL INVESTIGATIONS

Concentrations of the immunoglobulins A, G, and M were determined by nephelometry, and IgG subclass concentrations by immunodiffusion with specific polyclonal antibodies (Central Laboratory of the Netherlands Red Cross). Infants who had been followed up since birth were immunised at the ages of 3, 4, and 5 months with diphtheria toxoid, tetanus toxoid, and inactivated polio virus vaccine. To assess the humoral immune response, antitetanus toxoid antibodies were measured by an enzyme linked immunosorbent assay (ELISA) before and four weeks after the last immunisation. Infants entering the study after their primary immunisation but with antitetanus toxoid antibodies below 1000 U/l were given boosters of tetanus toxoid and the antibody response was reevaluated four weeks later. Antibody deficiency was defined as the lack of adequate antibody response (<1000 U/l) four weeks after immunisation.

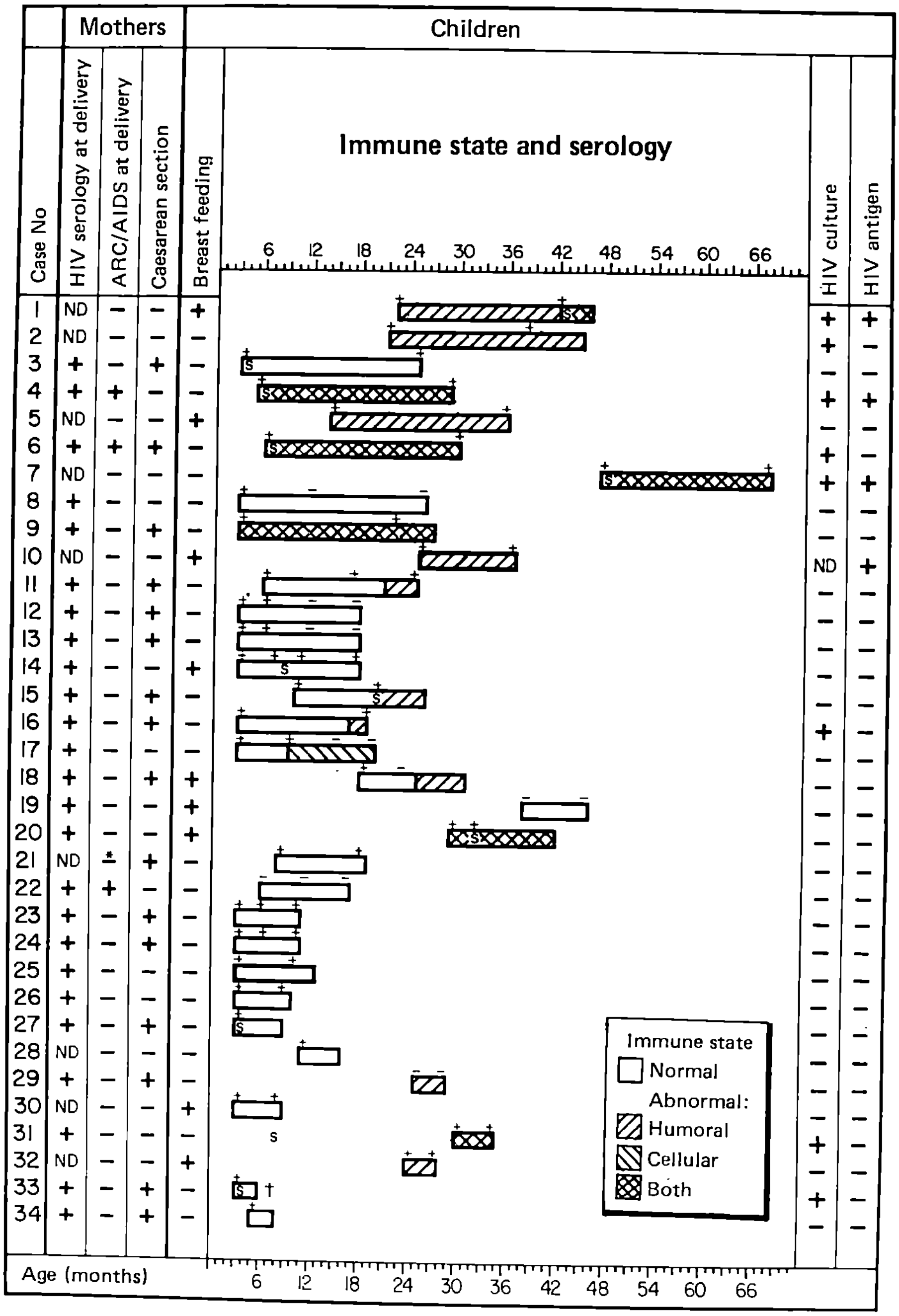
Cellular immunity was assessed by measuring lymphocyte subpopulations using specific monoclonal antibodies (Becton Dickinson) for surface IgM and IgD, CD4+ (T helper cell) and CD8+ (T suppressor cytotoxic cell) markers. Phytohaemagglutinin mitogen and tetanus antigen induced lymphocyte proliferation were measured by incorporation of tritiated thymidine four weeks after either primary immunisation or tetanus toxoid booster vaccination. Candidin was used as an additional antigen when there was extensive oral thrush. Skin tests were done with tetanus toxoid and candidin antigen using a commercial applicator (BioMerieux).

### VIROLOGICAL INVESTIGATIONS

Serological tests for antibodies of the IgG, IgM and IgA classes specific for HIV were done by western blot based on the biotin/avidin/horseradish peroxidase system using commercial strips (BioRad or DuPont). The strips were incubated with serum diluted 1:25. Human antibodies bound to HIV proteins were detected by the addition of biotinylated goat antibody specific for the heavy chains of the respective isotypes (Vector Laboratories) and then incubated with horseradish peroxidase H (Vector). The chromogenic substrate was 4-chloro-1-naphthol. To exclude the possibility that staining of the bands was by rheumatoid factors of the IgM or IgA classes binding to IgG antibodies specific for HIV, IgG was removed from test serum by absorption to Pansorbin (Calbiochem-Behring). Detection of HIV antigen (p24) in serum was by a commercial ELISA (Abbott Diagnostics Division). HIV was isolated as previously described.[2] Heparinised specimens of peripheral blood were passed over Ficoll-Hypaque gradients, and $1 \cdot 5 \times 10^6$ mononuclear cells were cocultured with $3 \times 10^6$ target cells consisting of either human peripheral blood mononuclear cells or of cord blood cells freshly isolated from normal donors seronegative for HIV. The target cells were grown for 48 hours in RPMI 1640 supplemented with 20% heat inactivated fetal bovine serum, phytohaemagglutinin (10 μg/ml; Sigma), and Polybrene (2 μg/ml; Sigma) before use. During coculture, cells were kept in RPMI 1640 containing 20% fetal bovine serum and interleukin 2 at a concentration of $2 \times 10^4$ U/l. Cells were refed every three to four days. Culture fluids were harvested at seven day intervals, pelleted at 100 000 g, and assayed for reverse transcriptase activity[6] and HIV antigen. Alternatively, the patients' mononuclear cells were prestimulated for two days with phytohaemagglutinin containing culture medium, before coculture with the target cells as described.[7]

## Results

From June 1986 to May 1988, 34 children (including two monozygous twin pairs and two siblings) born to 31 mothers were enrolled in the study (figure). The median age of the children at the time of writing was 25 months (range 6–68 months) and the mean observation period 13·4 months (range 3–24 months). Serology for HIV had been done for the mothers of 25 children before or at delivery. Three of the nine children whose mothers had not been tested before or immediately after delivery, were



| Case No | HIV serology at delivery | ARC/AIDS at delivery | Caesarean section | Breast feeding | HIV culture | HIV antigen |
|---|---|---|---|---|---|---|
| 1 | ND | − | − | + | + | + |
| 2 | ND | − | − | − | + | − |
| 3 | + | − | + | − | − | − |
| 4 | + | + | − | − | + | + |
| 5 | ND | − | − | + | − | − |
| 6 | + | + | + | − | + | − |
| 7 | ND | − | − | − | + | + |
| 8 | + | − | − | − | − | − |
| 9 | + | − | + | − | − | − |
| 10 | ND | − | − | + | ND | + |
| 11 | + | − | + | − | − | − |
| 12 | + | − | + | − | − | − |
| 13 | + | − | + | − | − | − |
| 14 | + | − | − | + | − | − |
| 15 | + | − | + | − | − | − |
| 16 | + | − | + | − | + | − |
| 17 | + | − | − | − | − | − |
| 18 | + | − | + | + | − | − |
| 19 | + | − | − | + | − | − |
| 20 | + | − | − | + | − | − |
| 21 | ND | −* | + | − | − | − |
| 22 | + | + | − | − | − | − |
| 23 | + | − | + | − | − | − |
| 24 | + | − | + | − | − | − |
| 25 | + | − | − | − | − | − |
| 26 | + | − | − | − | − | − |
| 27 | + | − | + | − | − | − |
| 28 | ND | − | − | − | − | − |
| 29 | + | − | + | − | − | − |
| 30 | ND | − | − | + | − | − |
| 31 | + | − | − | − | + | − |
| 32 | ND | − | − | + | − | − |
| 33 | + | − | + | − | + | − |
| 34 | + | − | + | − | − | − |

Figure *Synopsis of immune state and measurements of HIV infection in 34 children. Bars indicate observation period. *Died 28 months after delivery; †immune state not yet known; S=onset of symptoms; ND=not done.*

positive for HIV on culture (cases 1, 2, and 7), three had immune abnormalities (cases 5, 10, and 32), and three were younger than 15 months and still had anti-HIV antibodies (cases 21, 28, and 30). In one child (born to a mother who was seropositive for HIV at delivery) whom we saw first at the age of 25 months (case 19) no anti-HIV antibodies were detected. None of the 34 children received a blood transfusion.

### MATERNAL HISTORY

Twenty nine mothers were white and two were from the Caribbean. Intravenous drug abuse before (n=16) or during pregnancy, or both (n=10), was reported by 26 of the white mothers: the remaining three had HIV-seropositive partners. Neither the Caribbean mothers nor their Swiss husbands gave histories of drug abuse or of the transfusion of blood products. Seropositivity for HIV in these two men was found only after the serological state of their wives was known. The mean age of all mothers at delivery was 25 years (range 20–35). Three mothers had the acquired immunodeficiency syndrome (AIDS) or the AIDS related complex at delivery, and died 8, 15, and 16 months later, respectively. A fourth mother who was symptom free at delivery died of *Pneumocystis carinii* pneumonia 28 months later.

### PERINATAL HISTORY

Twenty one of the 34 children were boys and 13 girls. Their mean birth weight was 2858 g (range 1290–3950) and mean gestation 38 weeks (range 29–41). All birth weights and lengths were within the normal ranges for gestational age. Sixteen children were born by caesarean section. Symptoms of drug withdrawal were noted in nine of 13 children who were born to the 10 mothers who were intravenous drug abusers at the time of delivery. Eight infants were breast fed for a mean duration of 7 weeks (range 2–48).

### IMMUNOLOGICAL FINDINGS

Immune abnormalities were detected in 17 of 33 children (table 1, figure). In the remaining child, a 3 month old infant (case 33), immunological evaluation had not yet been done.

Four children (cases 4, 6, 7, and 31) already had symptoms by the time of the first visit and had humoral and cellular abormalities including hypergammaglobulinaemia (four of four) and decreased CD4+(T helper) cells (three of four). In all of them antibody deficiency and absence of an antigen specific cellular response in vivo and in vitro was registered after primary immunisation or boosting with tetanus toxoid. These four children were all positive on culture for HIV.

Three of the 13 remaining children with immune abnormalities developed symptoms during follow up: one by the time antibody deficiency was detected (case 15), and two only after hypergammaglobulinaemia, antibody deficiency, and absent in vivo and in vitro cellular response to tetanus toxoid had been discovered (cases 1 and 20). One of

Table 1 *Immunological findings*

| *Abnormalities of the immune system* | *Culture positive* | | *Culture negative, antibody positive at last test* | | *Culture negative, antibody negative* | |
|---|---|---|---|---|---|---|
| | *Symptoms of HIV infection** | *No symptoms* | *Symptoms of HIV* | *No symptoms* | *Symptoms of HIV infection* | *No symptoms* |
| Humoral: | | | | | | |
| Hypergammaglobulinaemia | 5/5 | 0/2 | 1/5 | 1/13 | 0 | 1/8 |
| $IgG_2/IgG_4$ deficiency in children over 24 months old | 1/5 | 1/2 | 1/5 | 3/13 | 0 | 0/8 |
| IgA deficiency in serum | 0/5 | 1/2 | 0/5 | 0/13 | 0 | 1/8 |
| Inadequate humoral response to tetanus toxoid | 4/5 | 1/2 | 2/5 | 2/13 | 0 | 2/8 |
| Cumulated abnormalities | 5/5 | 2/2 | 2/5 | 5/12 | 0 | 2/8 |
| Cellular: | | | | | | |
| CD4+(T helper) cells decreased | 3/5 | 0/2 | 0/5 | 0/13 | 0 | 0/8 |
| No response to in vitro testing with tetanus toxoid† | 5/5 | 0/2 | 1/5 | 1/13 | 0 | 1/8 |
| Cutaneous anergy | 5/5 | 0/2 | 1/5 | 1/13 | 0 | 1/8 |
| Cumulated abnormalities | 5/5 | 0/2 | 1/5 | 1/13 | 0 | 1/8 |

*One child not yet investigated; †if oral thrush was present candidin was also used.

the last two was also $IgG_2$ and $IgG_4$ deficient (case 1). He was infected with HIV on culture. The other two had anti-HIV antibodies persisting beyond the age of 15 months and met the Centers for Disease Control criteria of HIV infection.[8 9]

Two of the 10 children with immune abnormalities and no symptoms at the time of writing were positive on culture for HIV, one presenting with $IgG_2$ and $IgG_4$ and antibody deficiency (case 2), and the other with serum IgA deficiency (case 16). In five further children anti-HIV antibodies persisted beyond the age of 15 months: two had antibody deficiencies (cases 5 and 9), the first with additional $IgG_2$ and $IgG_4$ deficiency (case 5), and the second with no in vivo or in vitro cellular response to specific antigens. Two other children had hypergammaglobulinaemia (cases 10 and 11), and the fifth was $IgG_2$ and $IgG_4$ deficient (case 32). The last three of the 10 children with immune abnormalities and no symptoms at the time of writing lost anti-HIV antibodies and presented with hypergammaglobulinaemia and $IgG_2$ and $IgG_4$ deficiency (case 18), serum IgA and antibody deficiency (case 29), and no in vivo and in vitro cellular response to tetanus toxoid (case 17).

Four of the 16 children without immune abnormalities developed symptoms (cases 3, 14, 27, and 33). None was positive on culture for HIV, but two had anti-HIV antibodies persisting beyond the age of 15 months (cases 3 and 14).

### VIRUS CULTURE

HIV infection was confirmed in eight children by virus culture from peripheral mononuclear cells. Six of them developed symptoms (cases 1, 4, 6, 7, 31, and 33) (table 2), the other two (cases 2 and 16) being symptom free at the ages of 44 and 19 months, respectively.

### HIV ANTIGEN

Free HIV antigen (p 24) in serum was detected in three patients who were positive on culture for HIV (cases 1, 4, and 7) and in one patient aged 37 months who was symptom free (case 10), and in whom culture for HIV could not be carried out for technical reasons.

### ANTI-HIV ANTIBODIES

Up to the time of writing two children had lost IgG anti-HIV before 12 months of age (cases 8 and 22), three between 12–15 months (cases 12, 13, and 17), and one after 15 months (case 18). In two further

Table 2 *Clinical signs in the 11 children with symptoms*

| *Case No* | *Symptoms* | *Age at onset (months)* | *HIV culture positive* | *Anti-HIV antibodies* | | *Immune abnormality present* | | | | *Age at last visit (months)* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Present* | *Age (months)* | *Humoral* | | *Cellular* | | |
| | | | | | | | *Age diagnosed (months)* | | *Age diagnosed (months)* | |
| 1 | Diarrhoea, cough, lymphadenopathy | 42 | Yes | Yes | 42 | Yes | 22 | Yes | 42 | 46 |
| 3 | Diarrhoea | 3 | No | Yes | 25 | No | | No | | 25 |
| 4 | Oral candidiasis, hepatosplenomegaly, lymphadenopathy | 1 | Yes | Yes | 1 | Yes | 5* | Yes | 5* | 29 |
| | Failure to thrive | 5 | | | | | | | | |
| | Pneumonia, encephalopathy | 6 | | | | | | | | |
| 6 | Pneumonia, hepatosplenomegaly, lymphadenopathy, failure to thrive | 6 | Yes | Yes | 6 | Yes | 6* | Yes | 6* | 30 |
| | Encephalopathy, oral candidiasis | 10 | | | | | | | | |
| 7 | Cough | 47 | Yes | Yes | 48 | Yes | 48* | Yes | 48* | 68 |
| | Non-specific dermatitis | 66 | | | | | | | | |
| 14 | Oral candidiasis, diarrhoea | 12 | No | Yes | 18 | No | | No | | 18 |
| 15 | Developmental delay | 20 | No | Yes | 20 | Yes | 20 | No | | 26 |
| 20 | Lymphadenopathy | 32 | No | Yes | 18 | Yes | 29* | Yes | 29* | 42 |
| 27 | Spastic hemiparesis† | 3 | No | Yes | 3 | No | | No | | 9 |
| 31 | Thrombocytopenia | 8 | Yes | Yes | 8 | Yes | 9 | Yes | 29* | 35 |
| | Lymphadenopathy | 27 | | | | | | | | |
| 33 | Hyperexcitability | 3 | Yes | Yes | 3 | Not done | | Not done | | 6 |

*First visit to this unit; †probably a result of congenital toxoplasmosis, further investigation refused.

cases the age at which they lost their antibodies is unknown because they entered the study when they were already seronegative (cases 19 and 29).

Nine children who were negative on culture for HIV (and one in whom HIV culture could not be done) had persisting IgG anti-HIV after the age of 15 months (age range at last test 18–37 months). Seven of these 10 children (cases 5, 9–11, 15, 20, and 32) had immune abnormalities, two of whom had symptoms (cases 15 and 20). Of the three children without immune abnormalities (cases 3, 14, and 21) two had symptoms (cases 3 and 14).

In all eight children who were positive on culture for HIV, anti-HIV antibodies were present. Finally, the remaining eight (cases 23–28, 30, and 34) of the 34 children were younger than 15 months and still seropositive for HIV. One of them had symptoms, probably related to congenital toxoplasmosis (case 27).

The presence of HIV specific IgM antibodies was inconsistent. They were detected in five patients who were positive on culture for HIV (cases 1, 2, 4, 6, and 16); three of them lost the IgM at ages 12, 20, and 38 months, respectively. Specific IgM antibodies were also present in eight children who were negative on culture (cases 3, 10, 11, 14, 15, 20, 25, and 30) at ages 3, 3, 5, 9, 15, 15, 25, and 32 months, respectively. In three of them the result had been negative at earlier determinations (cases 10, 11, and 15). Five of the eight children negative on culture for HIV (cases 3, 11, 14, 25, and 30) lost the IgM later.

Specific IgA antibodies against HIV antigens were found inconsistently in three children who were positive on culture (cases 1, 4, and 6) and five who were negative on culture (cases 14, 21, 25, 27, and 30).

### CLINICAL SIGNS

The symptoms and their age of onset were noted in 11 children and are summarised in table 2. Two patients had AIDS (cases 4 and 6), three the lymphadenopathy syndrome (cases 1, 20, and 31), and in six children the symptoms may well have been caused by HIV infection (cases 3, 7, 14, 15, 27, and 33). Two of these six were positive on culture for HIV, a 68 month old girl and a 6 month old boy. He was hyperexcitable at the age of 3 months when his immune state still had to be assessed. A further three of the six children were older than 15 months and met the Centers for Disease Control criteria of HIV infection because of their seropositivity.[8 9] The sixth child presented with spastic hemiparesis (case 31) that was most probably due to congenital toxoplasmosis (serological data not shown). His foster parents refused further investigations.

Symptoms that may not have been caused by HIV occurred in one girl with humoral and cellular immune abnormalities and a positive culture for HIV (case 7), and in three children without immune abnormalities, two of whom met the Centers for Disease Control criteria for HIV infection[8 9] (cases 3 and 14), and one in whom HIV infection was still not certain (case 27). At the time of writing there had been no cancers and no deaths.

### TREATMENT

Daily antimicrobial prophylaxis with co-trimoxazole (40 mg/kg/day) and ketoconazole (5 mg/kg/day) and monthly infusions of intravenous gammaglobulin (0·4 g/kg) were started in five immunodeficient children with symptoms (cases 1, 4, 6, 20, and 31) at the ages of 45, 7, 10, 34, and 9 months, respectively. The favourable effect of this regimen in the two patients with AIDS and encephalopathy has been reported recently.[4] After the regimen was initiated we did not note any invasive bacterial or opportunistic infections.

## Discussion

Early diagnosis of HIV infection acquired prenatally or perinatally is crucial, because regular intravenous infusions of immunoglobulins have been successful in decelerating or stopping the progression of clinical disease, and slowing the decrease in immune competence.[4 10] Moreover, studies with antiviral drugs such as azidothymidine are currently under way. Diagnosis of infection is, however, obscured because serological testing is confused by the specific maternal IgG antibodies crossing the placenta and persisting for a period that is still not clearly defined. To overcome this obstacle, cumbersome methods are needed (such as virus cultures or lymphocyte cultures) for the detection of HIV itself or of in vitro synthesis of IgG specific for HIV.[11]

In the present analysis we concentrated on the diagnostic value of immunological assessment in children who were at risk of acquiring HIV infection from their mothers. The nature of the immune abnormalities that we found, including hypergammaglobulinaemia, antibody deficiency, IgG subclass deficiency, and in vivo and in vitro anergy, confirms the abnormalities reported elsewhere in paediatric journals.[12 13] Strikingly we found immune abnormalities not only in children with symptoms who were positive on culture for HIV but also in children who were symptom free but were either positive on culture for HIV or had anti-HIV antibodies persisting after the age of 15 months. Furthermore, immune abnormalities were also detected in three children who lost anti-HIV antibodies and in whom no other reason for the abnormalities could be

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found. This raises the question of whether these three children were infected or not, considering that loss of anti-HIV antibodies has been reported in children infected with HIV.[14]

The longitudinal design of the study enabled us to recognise the onset and the evolution of the immune abnormalities in a few cases. Based on our findings, the study population can be divided into three groups. One group comprised infants who developed symptoms of HIV within the first months of life; these infants already had immune abnormalities at the first examination. The second group comprised children in whom immune abnormalities were found but in whom symptoms, if any, emerged subsequently. These children were more likely to be infected (as proved on culture) or to have persisting anti-HIV antibodies after the age of 15 months. The third group comprised children without immune abnormalities; symptoms in these children, if any, did not seem to be clearly associated with HIV. Virus culture was always negative. Some of these children still had anti-HIV antibodies, but most had lost them.

Longitudinal assessment of immune state disclosed that humoral abnormalities—for example, hypergammaglobulinaemia and antibody deficiency, or $IgG_2$ and $IgG_4$ deficiency in children older than 24 months—usually preceded cellular immunodeficiency. In many children younger than 24 months we found $IgG_2$ and $IgG_4$ subclass deficiencies (data not shown). Because interpretation is difficult because of the lack of normal values from healthy individuals, this finding was not included in this analysis. Further immunological studies of more children must determine the consistency of this finding.

The Centers for Disease Control define HIV infection in children under 15 months by the presence of positive virus cultures, or of positive HIV serology associated with immunodeficiency and symptoms. In children older than 15 months, infection is defined by detectable anti-HIV antibodies alone. Using this definition, 19 of the 34 children studied would have to be regarded as infected. Eleven of these 19 had persisting antibodies after the age of 15 months. The negative virus cultures in these 11 children may be caused by the limited sensitivity of the method in symptom free subjects. Conversely, the high sensitivity of the western blot used[2] may have led to the detection of low amounts of maternal antibodies. Thus some children older than 15 months who are seropositive for HIV will not be infected, particularly those without immune abnormalities. On the other hand, loss of anti-HIV antibodies before or even after the age of 15 months does not exclude HIV infection.[14] Consequently, the presence of immune abnormalities in these children may be an early indicator of infection.

In conclusion, HIV serology alone may be misleading especially in symptom free infants older than 15 months. Additional assessment of their immune state comprising detailed analysis of antibody production and cellular immune responses after vaccination, as well as assessment of IgG subclass concentrations, may help in identifying infected children. These special immune abnormalities may be the first sign of active HIV infection. Detection of immune abnormalities also provides a useful indication for the initiation of antimicrobial prophylaxis or treatment—for example, with infusions of immunoglobulins. Measurement of antibody response to tetanus toxoid and skin testing are helpful in clinical practice, particularly when virus cultures or other cumbersome techniques cannot be performed. Careful immunological follow up of children born to mothers infected with HIV is important.

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# Pregnancy outcome at 24–31 weeks' gestation: mortality

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SUMMARY A study of all the mothers in the Northern region in 1983 whose pregnancies ended at between 24 and 31 weeks' gestation was undertaken. These pregnancies accounted for 1·3% of all the births and 44% of all the fetal and neonatal deaths in pregnancies that lasted more than 23 weeks. Most of the 389 singleton deliveries without malformations between 24 and 31 weeks were caused by spontaneous premature labour (n=119, 31%), placental abruption (n=79, 20%), pre-eclampsia (n=56, 14%), and premature rupture of membranes (n=48, 12%). The percentages of babies alive at the onset of delivery who survived the neonatal period were 66, 84, 78, and 73, respectively and the percentages of neonatal survivors with severe disabilities were 19, 13, 3, and 6, respectively. A further 65 (17%) of these babies died before the onset of labour for no obvious reason. The mode of delivery did not correlate with the outcome once the period of gestation at delivery was taken into account.

The results highlight the inadequacy of the perinatal mortality index currently used in the United Kingdom, which identified 10·7 deaths/1000 registered births in 1983; 20% of the babies delivered at 24–31 weeks were excluded by this index because the birth went unregistered, as were 21% of all the babies born alive who died before discharge. An index that accounted for all babies weighing 500 g or more at birth irrespective of the period of gestation, and all neonatal (0–27 days) deaths, would be more appropriate and would bring reporting more into line with recommended international practice.

At the request of interested clinicians, the Northern Regional Health Authority started a collaborative survey of perinatal mortality in 1980.[1] The survey was initially limited to stillbirths and early neonatal deaths, but later expanded to include late neonatal deaths; more recently late fetal deaths (after 21 weeks' gestation) have been included.

From the outset it was clear that as perinatal mortality fell pregnancies ending before 32 weeks' gestation were accounting for an increasing percentage of all perinatal deaths. Furthermore, even in pregnancies ending before 32 weeks' gestation, developments in neonatal care were transforming the outlook for babies who were born alive. Though intensive care was, however, undoubtedly reducing the number of early neonatal deaths, it was not clear whether it was preventing or merely delaying the deaths of some of the smaller babies. There was also increasing concern that many of the long term survivors might be severely disabled. A decision was therefore made when the survey was first started to monitor the long term outcome of some of the more vulnerable survivors.

A detailed review was undertaken of all pregnancies in the Northern region in 1983 in which delivery had occurred at 24–31 weeks' gestation. Some additional data were also collected about all pregnancies that resulted in a registerable birth in which the baby had weighed 1500 g or less at delivery whatever the period of gestation. These data on babies of <32 weeks' gestation and <1500 g birth weight were then reviewed together with information on the outcome of all deliveries to mothers normally resident in the region, using information provided by the regional perinatal mortality survey. The study is the outcome of a major voluntary effort by all the consultant obstetricians and paediatricians in the region. All could justly claim part authorship of the report: those whose names have been attached have merely assumed responsibility for the analysis of mortality, and for coordinating the assessment of survivors. The latter review forms the second report.[2]

## Subjects and methods

The Northern Regional Health Authority serves the whole of the north of England including the scattered rural communities of Northumberland, Durham, and Cumbria and the urban metropolitan counties of Tyne and Wear, and Cleveland. At the time of the survey 21 consultant obstetric units and five independent general practitioner units provided maternity services for a total population of just over 3 000 000.

The obstetric records of all mothers normally resident in the region who delivered at 24–31 weeks' (168–223 days) gestation, and the paediatric records of their babies, were examined. Numerous sources were used to ensure that all cases were recorded, and as an additional safeguard the details of all pregnancies recorded as ending at between 20 and 34 weeks' gestation and of all babies weighing less than 1501 g at birth were checked to ensure that gestational age was as stated. The admission registers of all gynaecology departments, delivery suites, and neonatal nurseries in the region were checked by a member of the team. Necropsy records were checked, and a particularly careful search was made for any aborted fetuses that had undergone necropsy. Lists of children were obtained from consultant paediatricians, community medical personnel, community nursing officers, and the regional child health computer system. The Regional Perinatal Mortality Register[1] provided information about all perinatal deaths.

### CASE NUMBERS

As soon as all the cases had been identified a cross check was undertaken with the data available to the Office of Population Censuses and Surveys (OPCS) and the Department of Health and Social Security (DHSS). The OPCS had identified three live births weighing $\leq$500 g, 100 live births weighing 500–999 g, and 210 weighing 1000–1499 g; the regional survey had identified two, 110, and 208, respectively. Transcription errors may have caused some problems with the data available to the OPCS, but part of the discrepancy was probably because no information was available about birth weight for 40 of the live births registered with the OPCS, and probably a disproportionate number of the smallest and illest babies were not weighed at birth. Data from the OPCS suggested that neonatal survival for liveborn babies who weighed less than 1000 g was 39 of 103 (38%), and the figure given by the DHSS, based on LHS 27/1 returns, was 42 of 103 (41%); the regional survey gave a validated figure of 49/112 (44%).

### BIRTH WEIGHTS

Discrepancies were occasionally encountered between the weight recorded in the obstetric notes and the weight recorded in the delivery suite register, the paediatric notes, and the nursery admission book, both for the babies who died, and for the survivors. Figures were frequently misread or transposed. The recording of weight of babies born dead was particularly inaccurate and it was clear from internal evidence that the recorded weight occasionally included the weight of the placenta as well as that of the fetus for some of the smaller babies. Registered weight of stillbirths did not always agree with the weight originally recorded in the case notes. Very small babies who underwent necropsy were measured more often than they were weighed. Some of the smaller babies were neither weighed nor measured.

### GESTATION

The recording of the period of gestation was even more inaccurate. Paediatric estimates of gestation times were rejected because no paediatric scheme for assessing gestation has ever been validated in babies born at less than 32 weeks' gestation. The estimates of the period of gestation used in this study are based on the antenatal recording of menstrual history and of uterine size at booking, together with any documentary evidence about quickening. All estimates were verified because errors had sometimes crept into the calculations in the case notes. Ultrasound information was used to estimate gestation in those pregnancies where the menstrual history was unreliable, but it was only used to modify the expected date of delivery in other cases where a reliable ultrasonographic estimate of fetal size at 12–18 weeks' gestation gave an estimate that differed from the menstrual estimate by more than 14 days. In the few pregnancies in which no reliable information was available or where it was difficult to reconcile two different estimates of gestation, an independent assessor was asked to determine gestation from a combination of the obstetric data, the information gained at necropsy, or clinical information regarding the child's neurological maturity at birth supplemented by information about when the baby first developed a reliable coordinated sucking and swallowing reflex. Information regarding the child's postneonatal progress was kept from the assessor to minimise potential bias.

CLASSIFICATION OF DEATH

All deaths were classified using a version of the scheme first proposed by Wigglesworth.[3] The obstetric factor most likely to have initiated the train of events leading to death was also assessed using a recently revised version of the classification used by Sir Dugald Baird[4] to analyse the data from the National Perinatal Mortality Survey of March 1958.[5]

## Results

There were 39 117 registered live births and 233 registered stillbirths in 1983, but 10 of the registered live births (who all died within a day) were delivered before 24 weeks' gestation and the survey identified a further 101 babies whose births were not registered because there was never any clear sign of life after delivery at 24–27 weeks' gestation.

The impact of antepartum and intrapartum fetal death, and of early and late neonatal death on the babies of 24–31 weeks' gestation are shown in fig 1, and table 1 shows the causes of death.[3] The 496 babies in fig 1 and table 1 represent 1·25% of all births to mothers in the region in 1983 for whom pregnancy lasted more than 23 weeks. The deaths ascribed to 'problems of prematurity' in table 1 were all caused by pulmonary immaturity or by hyaline membrane disease (surfactant deficiency) or its late consequencies (for example, bronchopulmonary dysplasia) with or without associated periventricular bleeding or confirmed secondary Gram negative bacterial pneumonia acquired while receiving respiratory support. In this classification[3] any death from a known fetal or neonatal cause (other than one obviously caused by immaturity) was classified as 'miscellaneous': the deaths included under this heading were 11 of infection, four of rhesus isoimmunisation, two of persistent transitional circulation, and one of necrotising enterocolitis.

The underlying obstetric factors that were thought to have set in train the events leading to the 248 fetal and neonatal deaths[4] are shown in fig 2. Maternal factors were identified in 13 of these deaths (in association with uterine abnormality, maternal illness, hypertension or renal disease antedating pregnancy, and symptomatic or asymptomatic maternal infection). The four deaths of rhesus isoimmunisation, the death of twin to twin transfusion, and the death caused by mechanical difficulty (cervical trapping of the head in an unattended breech delivery weighing 2200 g) have been grouped with the deaths due to maternal factors in fig 2.

LETHAL MALFORMATIONS

Twenty malformed babies of 24–31 weeks' gestation were classified as dead at birth, and a further eight died during the first week of life. Half the babies born dead were delivered before 28 weeks' gestation and were therefore unregistered; three of these were

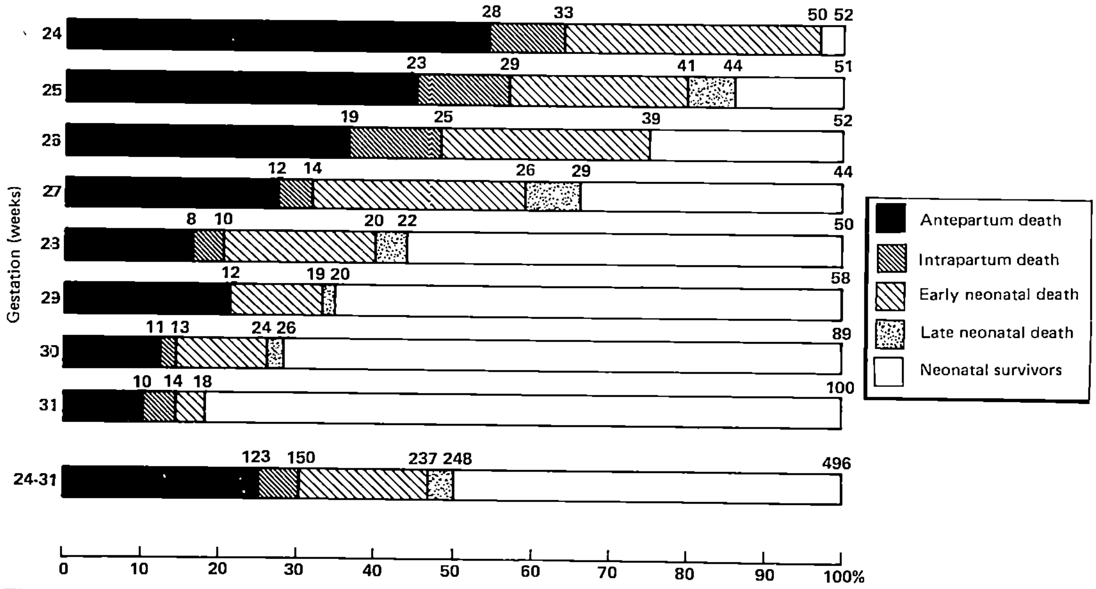

Fig 1 *The association between gestational age and the risk of antepartum, intrapartum, early (0–6 day), and late (7–27 day) neonatal death in the 496 babies of 24–31 weeks' gestation at delivery.*

Table 1 *Causes of fetal and neonatal death in babies of 24–31 weeks' gestation*

| *Gestation (weeks)* | *No of births* | | *Causes of death (singleton and plural births)* | | | | | *Neonatal survivors* | |
|---|---|---|---|---|---|---|---|---|---|
| | *Singleton births* | *Plural births* | *Malformation* | *Antepartum death* | *Intrapartum anoxia with or without trauma* | *Problems of prematurity* | *Miscellaneous causes* | *Singleton births* | *Plural births* |
| 24 | 36 (7) | 16 (7) | 7 (3) | 19 (7) | 5 (2) | 17 (2) | 2 | 1 | 1 |
| 25 | 46 (8) | 5 | 0 | 22 (7) | 6 | 13 | 3 (1) | 4 | 3 |
| 26 | 44 (4) | 8 | 2 | 17 (3) | 5 | 12 | 3 (1) | 11 | 2 |
| 27 | 40 (5) | 4 | 1 (1) | 11 (4) | 4 | 12 | 1 | 13 | 2 |
| 28 | 42 (2) | 8 | 6 | 8 (2) | 2 | 6 | 0 | 24 | 4 |
| 29 | 48 | 10 (1) | 4 | 10 (1) | 1 | 3 | 2 | 31 | 7 |
| 30 | 77 | 12 | 5 | 9 | 3 | 4 | 5 | 54 | 9 |
| 31 | 78 | 22 | 3 | 8 | 4 | 1 | 2 | 60 | 22 |
| Total | –11 (26) | 85 (8) | 28 (4) | 104 (24) | 30 (2) | 68 (2) | 18 (2) | 198 | 50 |

Numbers of babies weighing less than 500 g shown in parentheses.

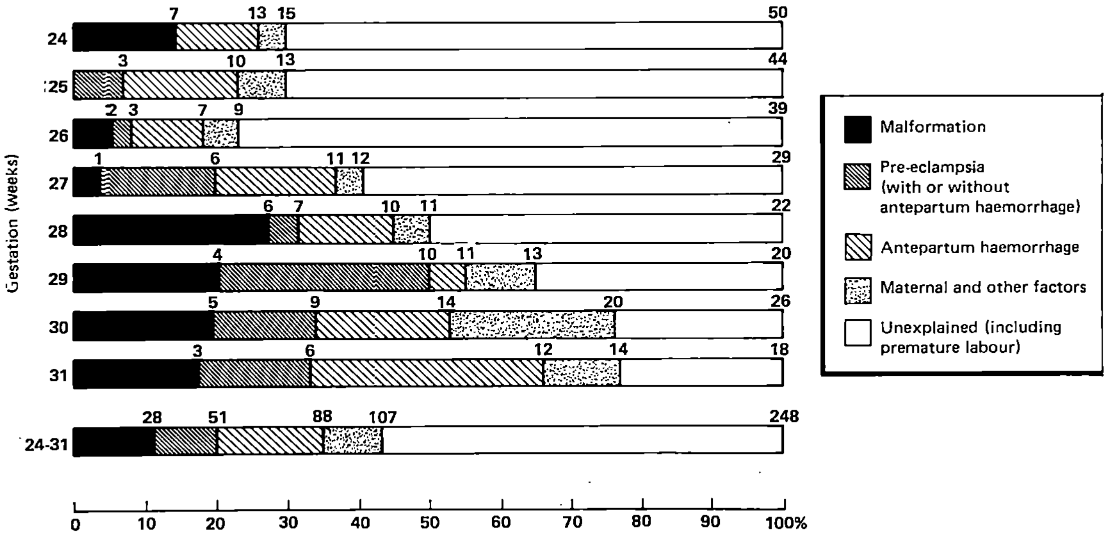

Fig 2 *Obstetric antecedents of fetal and neonatal death in the 248 babies of 24–31 weeks' gestation at delivery.*

legal terminations of pregnancy for known fetal abnormalities, and six of the 28 babies were twins. Thirteen had neural tube defects and four had bilateral renal agenesis or dysplasia.

### SINGLETON PREGNANCIES WITHOUT MALFORMATIONS

An analysis was undertaken to see to what extent the reason precipitating delivery (tables 2 and 3) or the mode of delivery influenced outcome as judged by neonatal survival, or by long term survival without disability two years after birth[2] in babies of 24–31 weeks' gestation.

### *Pre-eclampsia*

Twenty three percent (13 of 56) of the babies were born dead, 27% (12 of 45) of the babies who were alive at the onset of labour or delivery died before the age of 2 years or survived with severe disability, and one neonatal survivor was severely disabled. Six of the deaths that were associated with pre-eclampsia were also associated with antepartum haemorrhages.

### *Antepartum haemorrhage*

In the absence of pre-eclampsia this was usually caused by placental abruption but was occasionally associated with placenta praevia (seven mothers and three deaths). Thirty three percent (26 of 79) of the babies were born dead, 27% (15 of 55) of the babies who were alive at the onset of labour or delivery

Table 2 *The association between gestation and <28 day mortality in singleton babies without malformations*

| *Gestation (weeks)* | *Factor precipitating delivery*<br>*Pre-eclampsia with or without antepartum haemorrhage* | | *Antepartum haemorrhage* | | *Premature rupture of membranes* | | *Spontaneous premature labour* | | *Maternal factors* | | *Unexplained antepartum death* | | *Total* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *No of deaths* | *Total No* | *No of deaths* | *Total No* | *No of deaths* | *Total No* | *No of deaths* | *Total No* | *No of deaths* | *Total No* | *No of deaths* | *Total No* | *No of deaths* | *Total No* |
| 24 | 0 | 0 | 4 | 4 | 1 | 2 | 8 | 8 | 3 | 3 | 14 | 14 | 30 | 31 |
| 25 | 3 | 3 | 7 | 8 | 5 | 5 | 9 | 12 | 3 | 3 | 15 | 15 | 42 | 46 |
| 26 | 1 | 1 | 4 | 8 | 2 | 4 | 8 | 13 | 4 | 4 | 13 | 13 | 32 | 43 |
| 27 | 5 | 9 | 4 | 9 | 1 | 3 | 7 | 9 | 1 | 1 | 8 | 8 | 26 | 39 |
| 28 | 1 | 4 | 3 | 5 | 1 | 6 | 5 | 19 | 1 | 1 | 4 | 4 | 15 | 39 |
| 29 | 4 | 8 | 1 | 8 | 0 | 6 | 2 | 15 | 2 | 3 | 4 | 4 | 13 | 44 |
| 30 | 4 | 17 | 4 | 19 | 1 | 7 | 1 | 20 | 5 | 6 | 3 | 3 | 18 | 72 |
| 31 | 3 | 14 | 6 | 18 | 2 | 15 | 0 | 23 | 1 | 1 | 4 | 4 | 16 | 75 |
| Total | 21 | 56 | 33 | 79 | 13 | 48 | 40 | 119 | 20 | 22 | 65 | 65 | 192 | 389 |

Table 3 *Mortality and morbidity associated with the factor precipitating delivery in singleton babies without malformations*

| *Outcome of pregnancy* | *Factor precipitating delivery*<br>*Pre-eclampsia with or without antepartum haemorrhage* | *Antepartum haemorrhage* | *Premature rupture of membranes* | *Spontaneous premature labour* | *Other maternal factors* |
|---|---|---|---|---|---|
| Antepartum death | 11 | 24 | 0 | 0 | 5 |
| Intrapartum death | 2 | 2 | 0 | 11 | 2 |
| Neonatal death | 8 | 7 | 13 | 29 | 13 |
| Postneonatal death | 1 | 2 (2) | 5 (1) | 7 (5) | 0 |
| Long term survivors | 34 (1) | 44 (4) | 30 (1) | 72 (10) | 2 |
| Total | 56 (1) | 79 (6) | 48 (2) | 119 (15) | 22 |

Numbers of babies with severe perinatal disabilities shown in parentheses.

died before the age of 2 years or survived with severe disability, and 13% (six of 46) of the neonatal survivors had severe disabilities.

### *Premature rupture of membranes*

Rupture of the membranes without any immediate evidence of progressive labour was associated with 13 neonatal and five postneonatal deaths. Five of the neonatal deaths were due to group B β haemolytic streptococcal pneumonia and septicaemia, and secondary pulmonary hypoplasia associated with prolonged loss of liquor occurred in two of the others (not all the babies were examined for this at necropsy). Forty percent (19 of 48) of the liveborn babies died before the age of 2 years or survived with severe disabilities, but only 6% (two of 35) of the neonatal survivors had severe disabilities.

### *Unexplained spontaneous premature labour*

Forty seven percent (57 of 119) of the babies who were alive at the onset of labour died before the age of 2 years or survived with disabilities, and 19% (15 of 79) of the neonatal survivors had severe disabilities.

### *Other maternal factors*

There were six deaths caused by symptomatic or asymptomatic infection, and four deaths caused by rhesus isoimmunisation. Two mothers went into labour after undergoing laparotomies (one for appendicitis and the other for intestinal obstruction caused by adhesions), and the second of these babies survived without disability. Two babies were born dead and one survived caesarean delivery for severe maternal hypertension. One other baby was born dead following a maternal diabetic crisis, and another died of pulmonary immaturity shortly after delivery, when labour had started at 26 weeks' gestation in a mother with a double uterus and a past history of midtrimester miscarriage. Five early neonatal deaths at 24–26 weeks' gestation associated with unequivocal cervical incompetence have been included under this heading in table 2 (but classified as unexplained in fig 2 because the cause of the cervical incompetence was unknown).

*Mode of delivery*

We reviewed the association between mode of delivery and long term outcome in singleton pregnancies (excluding those in which the baby was lethally malformed or died before the onset of labour). Seventy two percent of the babies delivered by caesarean section survived to 2 years without severe disability, the prognosis being better when delivery was undertaken before rather than after the onset of labour (47 of 59 compared with 12 of 23). Fifty seven percent of the breech (25 of 44) and 52% of the vertex (82 of 159) vaginal births survived without severe disabilities. Twelve of the latter were delivered with forceps; all survived, but three had severe disabilities. One other baby survived compound presentation and delivery unscathed at 30 weeks' gestation. These figures give the impression that the outlook is better after operative abdominal delivery, but most of the babies delivered by caesarean section were relatively mature; only 18 (22%) were less than 29 weeks' gestation. An analysis taking gestation into account showed that outcome was only marginally better for babies delivered by caesarean section (table 4).

Table 4 *Long term survival without disability in singleton babies alive at the onset of labour or at delivery and without malformations*

| *Gestation (weeks)* | *Mode of delivery* | | | |
|---|---|---|---|---|
| | *Vaginal* | | *Caesarean* | |
| | *No of survivors* | *Total No* | *No of survivors* | *Total No* |
| 24 | 1 | 14 | 0 | 0 |
| 25 | 2 | 21 | 0 | 2 |
| 26 | 8 | 21 | 0 | 4 |
| 27 | 6 | 21 | 3 | 7 |
| 28 | 16 | 26 | 5 | 5 |
| 29 | 21 | 27 | 7 | 8 |
| 30 | 24 | 33 | 22 | 29 |
| 31 | 29 | 40 | 22 | 27 |
| Total | 107 | 203 | 59 | 82 |

PLURAL PREGNANCIES WITHOUT MALFORMATIONS

Labour started spontaneously at 25 weeks' gestation in the only triplet pregnancy. Two of the triplets died in the early neonatal period, and the other baby is a severely disabled long term survivor. There were a further 41 twin pregnancies. Thirty two of the 82 babies died in the perinatal period (12 were born dead before 28 weeks' gestation) and there was one late neonatal death (table 1). Six of the perinatal deaths were caused by lethal malformation. Perinatal mortality in twin babies (39%) was less than in singleton pregnancies (49%). Follow up data[2] also showed a reduction in the incidence of disability in twins surviving the neonatal period (three of 49 compared with 24 of 198), but this was not significant.

Unexplained spontaneous premature labour (22 mothers) and premature rupture of membranes followed later by the onset of spontaneous labour (six mothers) were commoner in twin pregnancies than in singleton ones. Fifteen of these babies died in the perinatal period, and two later in infancy. Two of the 39 survivors are severely disabled. Other complications of pregnancy were less common in twin pregnancies. Four mothers suffered placental abruption: four of the babies died in the perinatal period and one in later infancy, and one of the three long term survivors is severely disabled. One mother with pre-eclampsia of pregnancy lost both her babies in the neonatal period after delivery at 29 weeks' gestation. There were three unexplained antepartum deaths and twin fetal deaths with ascending uterine infection, while one other twin died of complications of the twin to twin transfusion syndrome. The twins born to two mothers at 31 weeks' gestation because of maternal hypertension that antedated pregnancy all survived.

## Discussion

CONTRIBUTION TO TOTAL FETAL LOSS

A review of the outcome of all pregnancies lasting more than 23 weeks in 1983 showed that 44% of all registered and unregistered fetal deaths, 63% of all early neonatal deaths, and 44% of all late neonatal deaths unassociated with lethal malformation occurred to babies born more than eight weeks before full term. Such deaths also accounted for half of all the deaths at any gestation associated with intrapartum anoxia or trauma, or both, in the absence of abruptio placentae and more than half of all the deaths associated with pre-eclampsia, antepartum haemorrhage, infection, and twin pregnancy.

FACTORS CAUSING DELIVERY BEFORE 32 WEEKS

It is often said that the development of an effective way of preventing or arresting spontaneous premature labour would be the biggest single contribution that could be made to reducing perinatal mortality. While this is true, spontaneous premature labour was responsible for only 29% of the singleton births (and 19% of the singleton deaths) at 24–31 weeks' gestation in this study: the contributions of placental abruption and other antepartum haemorrhage (19%), pre-eclampsia (14%), other maternal problems (4%), unexplained premature rupture of membranes (12%), fetal abnormality (5%), and rhesus isoimmunisation (1%) are often overlooked, as is that of totally unexplained antepartum fetal death (16%). Delivery was a planned and elective decision in only 14% (63 of 453) of all the mothers delivered before 32 weeks' gestation: the factor responsible for the decision to intervene was antepartum haemorrhage or hypertension (with or without signs of pre-eclampsia) in almost every case, together with supplementary evidence of poor fetal growth on seven occasions. These findings confirm the findings of a study from Oxford of the causes of preterm delivery.[6]

### SCOPE FOR IMPROVED CARE

There were 65 unexplained antepartum singleton deaths (table 2), and it is difficult to see what more could have been done to anticipate the deaths of most of these babies; six normally formed babies were small for gestational age but only one of these weighed 500 g or more at birth.

It is possible, however, that a few of the 11 antepartum deaths from pre-eclampsia might have been prevented by increased antenatal monitoring, because only three of these babies died before 29 weeks' gestation. General practitioners undertook the obstetric care of many of the women once the first booking visit to hospital was over until about 28 weeks' gestation. Pre-eclampsia often seemed to come on quite abruptly at about the time the women were preparing to return to the hospital clinic for further care, and some of the mothers had not seen a doctor or midwife for more than four weeks at the time of their admissions with severe pre-eclampsia. Enquiry suggested that uncertainty about the exact timing of the transfer back to hospital care and uncertainty about who was responsible for care during the transition period contributed to this oversight. It is at least possible that the onset of pre-eclampsia was sometimes less abrupt than it seemed to be.

Antepartum or intrapartum infection accounted for nine deaths, and postpartum infection for eight deaths (including five babies who became infected while being ventilated). Group B $\beta$ haemolytic streptococci were isolated from all five of the babies with antenatal infections in whom a positive microbiological diagnosis was made, and in each case there was a history of premature rupture of membranes. The resulting infections were uniformally fatal despite immediate treatment with antibiotics. In this series, therefore, lethal group B $\beta$ haemolytic streptococcal infection was identified in a tenth of all the singleton pregnancies in which the membranes had ruptured spontaneously before the onset of labour.

Five babies without malformations weighing 500 g or more died during labour or in the neonatal period as a result of intrapartum trauma, and 23 of intrapartum anoxia (table 1). Only five of the deaths of anoxia were associated with placental abruption. Few of the babies were monitored electronically during labour, partly because many of the mothers did not reach hospital until they were already in advanced labour, and it is at least possible that some lives could have been saved by increased monitoring and obstetric intervention. Only 18 babies in this study had caesarean deliveries after going into spontaneous labour in the absence of placental abruption and only 12 babies were delivered with forceps.

There is nevertheless nothing in these data to suggest that a general increase in operative delivery would improve outcome. The data in table 4 suggest only marginal benefit from caesarean delivery at any gestation. A larger study might confirm this trend, but this still would not establish that any difference in outcome was caused by the method of delivery itself. The prognosis for long term survival without disability among babies alive at the start of delivery was 73% among singleton pregnancies complicated by pre-eclampsia or antepartum haemorrhage, but only 54% in pregnancies complicated by premature rupture of membranes or spontaneous premature labour (table 3). Because pre-eclampsia or antepartum haemorrhage complicated 76% of the deliveries by caesarean section there can be no way of knowing whether it was the factor that influenced the obstetrician to choose caesarean delivery or the mode of delivery itself that contributed to the improved prognosis. Our conclusion concurs with that reached in the largest single centre study of the role of caesarean delivery in babies of less than 30 weeks' gestation.[7] Caesarean delivery was offered to 11% of all the babies of 24–29 weeks' gestation delivered in the Northern region in 1983 (the comparable figure from the Melbourne study being 15·6%).[7]

Improved resuscitation at birth might have saved a few lives. Twenty babies of 24–25 weeks' gestation born without malformations were never offered sustained respiratory support after birth, and a few of these might have survived had such facilities been available. Others who died from secondary complications precipitated by respiratory support after birth (such as pulmonary interstitial emphysema and bronchopulmonary dysplasia) might have survived had artificial surfactant and high frequency ventilation been available.

PERINATAL MORTALITY

The results of this study highlight the inadequacy of the current method of calculating perinatal mortality in the United Kingdom; 20% of the babies delivering at 24–31 weeks' gestation (101 of 496) would have been excluded from this study had those pregnancies in which a baby showed no clear sign of life after birth at 24–27 weeks' gestation been excluded from consideration merely because the birth did not legally need to be registered. Similarly, any study that ignored all deaths in babies over six days old would have ignored 21% (23 of 110) of the liveborn babies who died before discharge from hospital.

Perinatal mortality in the Northern region in 1983 among registerable births using the definition used by the OPCS was 10·7 deaths/1000 births (423/39350). Any calculation, however, that took into consideration all pregnancies lasting more than 21 weeks' gestation (in line with the recent report issued by the Royal College of Obstetricians[8]) would have produced a figure of 15·9/1000 births (627/39544) for perinatal mortality because in addition to the 101 babies born dead at 24–27 weeks' gestation (fig 1), 103 babies (including 10 twins) were delivered at 22–23 weeks' gestation, and only seven of these babies were registered as live born. Similarly, any calculation using the definition recommended by the World Health Organisation,[9] which identifies all babies weighing 500 g or more at birth irrespective of period of gestation, would have yielded a figure of at least 12·6/1000 births (497/39424)[2]—the exact figure being uncertain because some babies of less than 24 weeks' gestation went unweighed. When account is taken of the 46 late neonatal deaths among babies born in the region in 1983, an overall perinatal and late neonatal mortality rate of at least 13·8 deaths/1000 births is obtained for babies weighing 500 g or more at birth. Babies of less than 32 weeks' gestation accounted for 45% of these deaths.

Others have highlighted this issue before.[10] Survival is becoming increasingly common at 24–27 weeks' gestation, and it is now widely accepted that the clinical limit of viability is nearer to 24 weeks' than 28 weeks' gestation. The method of calculating perinatal mortality currently in use in the United Kingdom has little in its favour (except that it can be used to compare current rates with past data). The definition bears little relation to that recommended by the World Health Organisation and, as low birthweight deaths account for a progressively larger percentage of all deaths, the discrepancy becomes increasingly unacceptable. International comparison is impossible and the lack of data on babies born dead before 28 weeks' gestation renders comparison across this gestational divide meaningless.

A commitment to registering the delivery of every baby born after more than 21 weeks' gestation would give a more appropriate index of fetal loss. It would also serve to acknowledge the sense of loss that parents feel after a late miscarriage. It would need to be accompanied, however, by a commitment to weigh every baby at birth and record the birth weight together with the other confidential particulars collected on every birth at registration. While the present survey managed to obtain this information, the effort that this entailed only serves to highlight the fact that such information will never become generally available until its collection becomes a legal necessity.

The time has come to reform the method of assessment of perinatal mortality in this country, or to tacitly admit by our inaction that it is not a statistic that particularly matters.

This report is published with the agreement of the survey steering group, but we take full responsibility for the content. We thank the obstetricians and paediatricians whose continuing support for the region's collaborative Perinatal Mortality Survey made this study possible. We also thank Mrs M Renwick, the survey coordinator, whose commitment and efficiency made sure that no relevant death went undocumented.

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# Pregnancy outcome at 24–31 weeks' gestation: neonatal survivors

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SUMMARY All surviving babies of less than 32 weeks' gestation born to mothers resident in the Northern region in 1983 were assessed. No baby was lost to follow up, and 230 long term survivors were assessed when 2 years old, by a single observer. Among 248 neonatal survivors, severe disability was present in 10 of the 37 at 24–27 weeks' gestation (27%) and in 18 of the 211 at 28–31 weeks' gestation (9%). On average the surviving babies required 27 days and seven days of intensive care nursing respectively. Babies who were ventilated for more than two weeks and babies who had neonatal fits had a poor prognosis. Because of postneonatal deaths only 20 of the 230 long term survivors of <32 weeks' gestation were severely disabled (9%).

Comparable data were obtained for all babies weighing 1500 g or less at birth, irrespective of their gestational age. Severe disability was seen in eight of the 49 neonatal survivors (16%) who had weighed 500–999 g at birth, and in 17 of the 171 survivors (10%) who had weighed 1000–1499 g. The 10 neonatal survivors who had weighed exactly 1500 g at birth were all well. Only 18 of the 212 long term survivors (8%) who had weighed 1500 g or less at birth were severely disabled.

Because the period of gestation is the only variable known to the obstetrician before delivery, and disability correlates better with gestation than birth weight, future studies should concentrate on relating morbidity, mortality, and the cost of neonatal care to gestation rather than weight at birth.

There have been many publications about the long term prognosis for low birthweight babies. Most have concerned the experience in a single hospital, and reported accumulated data over a number of years. Few have reported the outcome in an unbiased population of all the babies born to mothers living in a defined geographical area in a defined time. Fewer still have provided detailed analyses of all the deaths as well as of disabilities among survivors from such a cohort. No such study has managed to maintain contact with every survivor for two years so that a single clinician could assess the progress of every child consistently.

A study has now been completed in the Northern region of all very low birthweight babies born in 1983. Comparable studies of children born before 1980 had all reported outcome in terms of birth weight, but gestation is the only variable accurately known to the obstetrician before delivery. We therefore report here the developmental progress of every baby born before 32 weeks' gestation in 1983, as well as the outcome for every neonatal survivor who had weighed 1500 g or less at birth.

## Subjects and methods

Background information had already been collected (for a parallel study of mortality) for every baby of less than 32 weeks' gestation and every baby weighing 1500 g or less at birth born in 1983 to a mother normally resident in the Northern region.[1] Approval for a special follow up survey was obtained from each district's ethics committee. All the children were traced and seen by a single clinician (UW) for assessment on or about their second birthday (21–26 months after birth) in order to make the assessments as consistent as possible. Information from the general practitioners, health visitors, and local paediatricians was available to the doctor before he saw each family, but information about the obstetric and neonatal background was only abstracted from the hospital case notes and entered on a standard form after the assessment had been completed.

Objective measures of disability were obtained so that this study could be compared with similar studies, although precise testing can be difficult in children only 2 years old especially if they are shy, restless, or uncooperative. Assessment included a full medical history followed by a complete clinical and neurological examination, including anthropometric measurements and the recording of the blood pressure. A Griffiths's assessment[2 3] was made to obtain a quantitative assessment of developmental progress. Stycar hearing tests were supplemented by free field audiometry in the more cooperative children, and binocular visual acuity was checked with Stycar tests; in half the children this was repeated for each eye separately. The visual fields were checked, and a cover test was done for latent squint. More detailed audiological and ophthalmic information was obtained on all the children with any significant impairment. The clinical findings were always discussed with the parents as soon as the assessment was complete, and arrangements made for further help to be obtained on those occasions where this assessment brought a clinical problem to light for the first time.

## Results

There were 39 350 registered births in the Northern region in 1983; 395 of these babies were born before 32 weeks' gestation. There were also 101 babies who were born dead at 24–27 weeks' gestation and whose births were not registered. There were 49 registered stillbirths and 346 live births before 32 weeks' gestation. Eighty seven of the live born babies died in the first week of life, 11 more died during the next three weeks, and 18 died later in infancy.[1] There were therefore 230 long term survivors from this cohort two years after delivery (table 1).

### POSTNEONATAL DEATHS

There were 18 postneonatal deaths (table 2). Eight of these babies had clinical evidence of severe perinatal neurological impairment before death, and this clinical assessment was supported by ultrasound or necropsy evidence of severe parenchymal brain damage, or both, except in the one case where no ultrasound or necropsy examination was undertaken. Six of the 18 babies died after leaving hospital, and only one of these had an impairment that looked as though it was likely to cause disability; all were dead within seven months of delivery.

### LONG TERM SURVIVORS

The detailed developmental progress of the 230 children still alive two years after birth is summarised in fig 1. Every child with a developmental quotient of less than 70 also had other grounds for being classified as severely disabled. The developmental quotient of the children of more than 26 weeks' gestation who had no motor or sensory disability was normally distributed, but the babies of 24–26 weeks' gestation tended to have a slightly lower developmental quotient—a finding that will call for further scrutiny when the children reach school age.

### *Severe disability*

Cerebral palsy severe enough to hamper physical activity appropriate to the child's age was judged a severe disability, as was deafness severe enough to warrant a hearing aid (usually equivalent to a hearing loss of 50 dB or more in the better ear), and blindness or partial sight (usually equivalent to a corrected binocular visual activity of 6/60 or less). A developmental quotient of less than 70 on the Griffiths's assessment scales was also accepted as evidence of severe disability. This threshold was chosen because it is three standard deviations below

Table 1 *Mortality and morbidity in babies of 24–31 weeks' gestation*

| *Gestation (weeks)* | *Deaths* | | | *Survivors at the age of 2 years* | | | |
|---|---|---|---|---|---|---|---|
| | *Born dead* | *Neonatal deaths (0–27 days)* | *Post-neonatal deaths†* | *Severe disability* | *Impairment without disability* | *Minor impairment* | *Normal* |
| 24 | 33* | 17 | 1 (0) | 0 | 0 | 0 | 1 |
| 25 | 29* | 15 | 1 (1) | 2 | 0 | 1 | 3 |
| 26 | 25* | 14 | 1 (1) | 2 | 1 | 1 | 8 |
| 27 | 14* | 15 | 2 (1) | 3 | 0 | 1 | 9 |
| 28 | 10 | 12 | 2 (1) | 2 | 0 | 2 | 22 |
| 29 | 12 | 8 | 2 (1) | 2 | 3 | 4 | 27 |
| 30 | 13 | 13 | 4 (2) | 3 | 2 | 7 | 47 |
| 31 | 14 | 4 | 5 (1) | 6 | 2 | 7 | 62 |
| Total | 150 | 98 | 18 (8) | 20 | 8 | 23 | 179 |

*Unregistered stillbirths; †number with neurodevelopmental impairment in parentheses.

Table 2 *Postneonatal deaths among babies of <32 weeks' gestation or weighing ≤1500 g at birth*

| *Gestation (weeks)* | *Birth weight (g)* | *Sex* | *Mode of delivery* | *Reason delivered* | *Ventilation (days)* | *Age at death (days)* | *Diagnosis* |
|---|---|---|---|---|---|---|---|
| 24 | 660 | F | Breech | Premature labour | 31 | 31 | Necrotising enterocolitis, chronic lung damage; twin |
| 25 | 800 | M | Vertex | Premature labour | 48 | 48 | Necrotising enterocolitis, terminal candida septicaemia, severe posthaemorrhagic hydrocephalus* |
| 26 | 1110 | F | Caesarean | Abruption | 25 | 118 | Staphylococcal ventriculitis after shunt for posthaemorrhagic hydrocephalus* |
| 27 | 980 | M | Vertex | Abruption | 16 | 36 | Klebsiella meningitis: periventricular leucomalacia at necropsy* |
| 27 | 995 | M | Breech | Premature rupture of membranes | 18 | 41 | Resuscitation failed after sudden apnoeic attack |
| 28 | 670 | M | Breech | Premature labour | 30 | 178 | Chronic lung damage after ventilation; twin |
| 28 | 1200 | M | Vertex | Premature rupture of membranes | 34 | 34 | Persistent seizures. No necropsy* |
| 29 | 1190 | F | Vertex | Premature rupture of membranes | 11 | 138 | Home after 65 days; died of respiratory syncytial bronchiolitis |
| 29 | 1400 | M | Vertex | Premature labour | 14 | 118 | Home after 91 days; periventricular leucomalacia; died suddenly at home* |
| 30 | 965 | M | Caesarean | Toxaemia | 62 | 62 | Ventilator dependent from birth; chronic lung damage |
| 30 | 1300 | M | Caesarean | Premature labour | 3 | 37 | Died after operation for necrotising enterocolitis. Intracerebral haemorrhage with fits* |
| 30 | 1490 | M | Vertex | Premature rupture of membranes | 17 | 185 | Chronic lung damage after ventilation |
| 30 | 1660 | M | Vertex | Premature labour | 31 | 37 | Citrobacter septicaemia, intracerebral bleed* |
| 31 | 1130 | M | Caesarean | Abruption | 32 | 103 | Home after 91 days: died after sudden apnoeic attack. Twin |
| 31 | 1340 | F | Vertex | Premature labour | — | 205 | Home after 43 days: cot death |
| 31 | 1380 | M | Breech | Premature labour | — | 181 | Home after 64 days: cot death |
| 31 | 1400 | F | Vertex | Premature rupture of membranes | — | 83 | Home after 49 days: cot death |
| 31 | 1775 | M | Vertex | Maternal factors | 30 | 101 | Staphylococcal meningitis while undergoing tap for posthaemorrhagic hydrocephalus* |
| 32 | 1280 | M | Vertex | Premature labour | 5 | 129 | Concealed birth; subdural haemorrhage, died of fits* |
| 33 | 1480 | F | Caesarean | Toxaemia | 16 | 44 | Cardiac failure; also had rectal agenesis and cardiac defect |

*Had severe perinatal neurological impairment.

the mean and identifies continuing serious developmental delay in later childhood with some certainty. We would have classified epilepsy uncontrolled by drugs, chronic malabsorption and growth retardation due to major bowel resection, the loss of a limb, or the presence of a permanent stoma as severe disabilities, but did not find any.

Twenty children were severely disabled, and most of these children had more than one disability (fig 1). Fifteen children had disabling cerebral palsy, and 12 had developmental quotients of less than 70. Seven children were registered as blind or partially sighted; in four cases this was caused by damage to the central visual pathways, but in three there was severe retinopathy of prematurity. The five children with cerebral palsy as well as visual disability had the lowest developmental quotients in the study. Four children were deaf enough to require hearing aids, but none of the deaf children had had serum bilirubin concentrations of more than 225 μmol/l, and only one (a profoundly disabled child of 31 weeks' gestation) had any features of cerebral palsy. Three children had serious epilepsy, but in each case this was well controlled by drugs.

These definitions identify a group of children who had cerebral palsy severe enough to interfere with everyday motor activity, or sensorineural impairment severe enough to be likely to require special educational provision, or both. Nine children had developmental quotients of less than 50. Poor outcomes had been anticipated in some of these children. The only surviving triplet baby (of 25 weeks' gestation) required considerable resuscitation at birth and had early evidence of intracerebral bleeding on ultrasound scan followed by diffuse cystic change (developmental quotient 30). One child had congenital myotonic dystrophy and a developmental quotient of 38, and another had been ventilated for severe coliform meningitis at the age of 5 days (developmental quotient 22). Four other babies, however, had remarkably uneventful neonatal courses: two were ventilated for less than four days (developmental quotients 11 and 41) and two were not ventilated at all (developmental quotients 8 and 41). Some disability had been anticipated in the remaining two babies because there was ultrasound evidence of intracerebral bleeding (developmental quotients 10 and 18), but

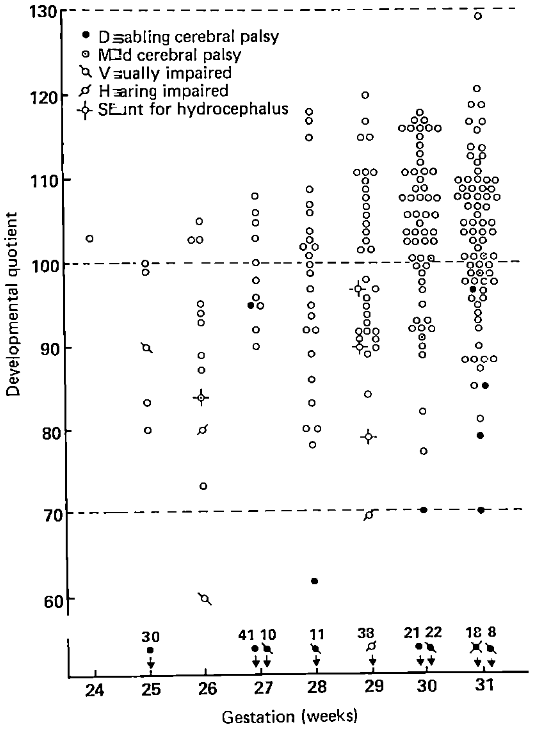

Fig 1 *Association between gestation and developmental quotient in all the babies who survived to the age of 2, showing the correlation with other sensorineural impairment. Numbers refer to individual developmental quotients of babies scoring less than 60.*

the neonatal courses of these two children did not otherwise differ from those of some of the children who were much less disabled.

*Impairment without disability*

Eight children had impairment without disability: five had definite but mild cerebral palsy (usually mild hemiplegia) and four had required ventriculoperitoneal shunts because of posthaemorrhagic hydrocephalus, but were otherwise well without any important neurological disability. Only one had a developmental quotient below 80 (fig 1).

*Minor impairment*

A further 23 children had minor impairments. Problems under this heading included squint (n=17), growth retardation after resection of bowel and temporary ileostomy (n=2), severe amniotic bands or talipes requiring operation (n=2), pronounced speech delay with probable conductive hearing loss (n=1), and longstanding ankylosis of both elbows (n=1).

*Uncategorised mild developmental delay*

Three children without pronounced motor or sensory impairment had developmental quotients of between 70 and 79 when seen at the age of 2 years (that is, quotients two to three standard deviations below normal). All had deprived backgrounds; in addition, one child had been encased in plaster for late diagnosed congenital dislocation of the hip for more than 12 months, one child's mother had suffered a long severe depression, and the third child came from a family where there had been child abuse. Two of the three children with developmental quotients of 80 had also received little stimulation, and one had spent more than eight months in hospital (fig 1). The effect of the environment on development becomes progressively more important with time, and some or all of these children may need special educational provision in due course. A low assessment quotient at this age, however, may merely mean that the child was shy and uncooperative in unfamiliar surroundings when tested. All the children in this study will be reviewed again at the age of 6 to monitor their growth, validate the assessment of disability made at the age of 2, and look for signs of poor motor coordination and other important but subtle learning problems.

*Babies small for gestational age*

The distribution of birth weight by gestation in this community based study was similar to that recently reported for a hospital based study from Oxford.[4 5] Thirteen normally formed babies who were born dead had weights below the fifth centile at delivery, as did three babies who died shortly after birth. Ten babies with weights below the fifth centile survived the neonatal period, though one died later of lung damage after a period of prolonged respiratory support (table 1). The nine long term survivors were well at two years, without any disability or impairment. Others have reported, however, that babies small for gestational age who weighed 1500 g or less at birth often perform poorly in school.[6] Similar findings have been reported in babies small for gestational age who were born at full term where there was sonar evidence that fetal growth had started to falter before 27 weeks' gestation.[7] It will be particularly important, therefore, to reassess these children after they have started school.

*Predicting neonatal outcome*

There was only a marginal excess mortality among boys, but 22 of the 28 neonatal survivors with disability were boys, and a preponderance of boys has been noted in other studies.[8] Overt neonatal fits[9] were also strongly correlated with severe disability: seven of the 17 neonatal survivors who had fits in the first week of life died later in infancy with evidence of severe perinatal neurological impairment, and five long term survivors are also disabled. One other baby survived with a mild left hemiplegia; only four seemed entirely well when 2 years old. Babies ventilated for up to two weeks were only slightly more likely to survive with disability than babies not ventilated at birth (9% compared with 5%), but babies ventilated for more than two weeks had a high risk of disability (table 3).

There seemed to be no correlation between the highest serum concentration of bilirubin recorded in the neonatal period and the risk of disability among long term survivors. Thirty three survivors had had serum bilirubin concentrations of 250 μmol/l or more, but only two of these children were disabled: both had severe spastic quadriplegia and one was also blind but neither was deaf. Two of the three children with disabling retinopathy of prematurity were of less than 27 weeks' gestation and both had received supplemental oxygen for more than 10 weeks (this was also true, however, of 10 children who had no visual problems at follow up); the third child (of 30 weeks' gestation) with retinopathy of prematurity had been ventilated for eight days and given supplemental oxygen for 14 days after developing meningitis when 5 days old.

### HOSPITAL CARE

Figure 2 shows how gestational age influenced the amount of hospital care received by the babies of less than 32 weeks' gestation who died before discharge, and by the survivors. The times spent receiving intensive care (respiratory support) and high dependency care are shown separately because staffing needs make such care particularly expensive.[10] The babies of less than 32 weeks' gestation accounted for 6% of all admissions to special care units but 29% of all nursery cot occupancy in the region during the year of the survey. Three quarters of all the babies ventilated in the region during the year were of less than 32 weeks' gestation, and these babies accounted for 84% of all non-surgical neonatal ventilator usage ('ventilator nights'). Only 4% (two of 57) of the liveborn babies of 26–27 weeks' gestation and 27% (23 of 86) of liveborn babies of 28–29 weeks' gestation survived without sustained respiratory support (fig 2), but 58% (94 of 162) of babies of 30–31 weeks' gestation survived without support, as did 86% of the babies of 32–33 weeks' gestation.

### SURVIVORS OF ANY GESTATIONAL AGE WHO WEIGHED LESS THAN 1500 G AT BIRTH

A separate analysis was undertaken of the outcome

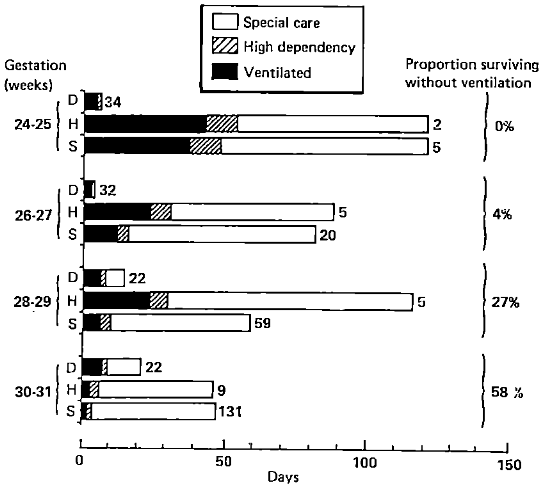

Fig 2 *Association between gestational age and average hospital care needs of babies who died before discharge (D) and in the disabled (H) and non-disabled (S) survivors, with care classified in a comparable way with previous costing studies.[10] The numbers at the end of each histogram bar indicate the number of babies in each group.*

Table 3 *Correlation between ventilation dependency in days and the risk of severe disability in those who survived for 28 days*

| *Outcome* | *No of days ventilated* | | | | | |
|---|---|---|---|---|---|---|
| | *0* | *1–6* | *7–13* | *14–20* | *21–27* | *≥28* |
| No of survivors at 28 days | 121 | 56 | 31 | 11 | 7 | 22 |
| No of later deaths: | | | | | | |
| Disabled | 0 | 1 | 0 | 2 | 1 | 4 |
| Not disabled | 3 | 0 | 1 | 2 | 0 | 4 |
| No of disabled long term survivors | 6 | 4 | 2 | 1 | 1 | 6 |
| Percentage of neonatal survivors disabled | 5 | 9 | 6 | 27 | 30 | 45 |

for all babies who had weighed 1500 g or less at birth, whatever their gestational age. There were nine registerable births of less than 500 g, two at 20–23 weeks' gestation, four at 24–31 weeks' gestation, and three at more than 31 weeks' gestation, but none of these babies survived the neonatal period. A further 470 babies weighed between 500 and 1499 g at birth (table 4). Details of the postneonatal deaths are given in table 2. Nine babies of 24–31 weeks' gestation and four babies of more than 31 weeks' gestation weighed exactly 1500 g at birth. One baby was stillborn at 37 weeks' gestation, and two babies died with lethal malformations on the first day of life at 28 and 30 weeks' gestation, respectively. The 10 survivors were all well without disability, when 2 years old.

One hundred and eight babies (including 82 neonatal survivors) of 24–31 weeks' gestation weighed 1500 g or more at birth, and 96 babies (including 54 survivors) weighed less than 1500 g, although they were more than 31 weeks' gestation at birth.

## Discussion

Every neonatal survivor in this large regional study was accounted for, and every child assessed by the same observer when 2 years old. Some children proved difficult to trace, and others proved difficult to see for assessment though they were traced without difficulty. The amount of disability in these latter groups was much higher than in the 89% who were contacted without difficulty,[11] a finding that points to the importance of tracing and assessing all the survivors in any study of this nature.

Table 4 *Outcome at the age of 2 of all babies weighing 500–1499 g at birth who were born in the Northern region in 1983, irrespective of period of gestation*

| *Outcome* | *Birth weight* | |
|---|---|---|
| | *500–999 g* | *1000–1499 g* |
| No of babies born dead before 28 weeks' gestation | 80 | 3 |
| No of registered stillbirths | 23 | 46 |
| No of neonatal deaths (0–27 days) | 61 | 37 |
| No of later deaths: | | |
| Disabled | 2 | 5 |
| Not disabled | 4 | 7 |
| No of disabled long term survivors | 6 | 12 |
| No of other long term survivors | 37 | 147 |
| Percentage disability in long term survivors | 14 | 8 |

POSTNEONATAL DEATH

Eighteen of the 248 babies of less than 32 weeks' gestation who survived the neonatal period died later (7%). Six died suddenly, five after discharge from hospital; one neurologically impaired baby probably died of a seizure shortly after discharge but the other five deaths were unexplained, though one baby did have some evidence of bronchopulmonary dysplasia at necropsy. It seems that the risk of sudden infant death in babies born more than eight weeks early may be 10 times as high as in babies born at full term.[12] Most of the other postneonatal hospital deaths were caused by infection, chronic lung scarring after a period of respiratory support, or necrotising enterocolitis (table 2).

TWIN PREGNANCIES

Mortality among twins delivered before 32 weeks' gestation was slightly lower than in singletons of comparable gestation in this study[1] as it was in the National Perinatal Mortality Survey of 1958.[13] The incidence of disability among survivors was also less than among singletons. This finding is in keeping with other work, suggesting that when twin babies are compared with singletons and matched for gestation a clear excess of cerebral palsy is only seen in comparatively mature twins.[14] The risk of fetal or early neonatal death in a twin pregnancy of more than 21 weeks' gestation was 10 times as high as it was in singleton pregnancies in this study, largely because of the increased risk of premature labour. Forty six of the 413 twin pregnancies (11%) ended before 32 weeks' gestation in 1983, and 42 of 70 (60%) of the perinatal mortality associated with twin pregnancy occurred among these babies. Indeed, 53% of all fetal and early neonatal losses occurred before 29 weeks' gestation, including all but four of the 19 neonatal deaths associated with problems of prematurity. Even if there is any benefit in offering bed rest in twin pregnancies[15] it would seem to be illogical to delay it until 32 weeks' gestation.

COST

Much concern has been expressed over the cost of providing medical care for babies as small as this, and studies from North America have suggested that the cost may outweigh the economic benefit for babies weighing below about 1000 g (if this is calculated in purely monetary terms). Costing exercises in this country have failed to define a particular birth weight below which it is uneconomical to offer sustained intensive care support, but they have identified that the average investment put into caring for the babies who did not survive to discharge can be nearly as high as that put into the care of survivors.[10]

No attempt has been made to undertake a full detailed costing of neonatal care in this study, but a realistic estimate can be obtained from a knowledge of cot occupancy and the length of time for which each child required respiratory support or received other high dependency care. On the assumption that the care of the babies requiring respiratory support costs about three times as much as that of babies only requiring special care[10] it can be seen that the 110 babies who failed to survive to discharge accounted for only about 12% of the sum spent on caring for all the liveborn babies of 24–31 weeks' gestation before discharge. If babies who failed to survive for at least a day after birth are discounted (as in previous costing studies) the average amount invested in each of the 57 babies who did not survive to discharge is still only a quarter of that invested in the 236 babies who did. Only in babies of 30–31 weeks' gestation did the care invested in the 16 babies who survived more than a day but who failed to survive to discharge exceed the average spent on the 140 babies who did survive to discharge.

Previous costing studies have failed to show any strong correlation between cost and birth weight,[10] but the data in fig 3 suggest that there is quite a strong correlation between cost and gestational age, and this is further strengthened when individual (rather than average) care costs are analysed. This is of course what would be expected, because very premature babies are usually only robust enough for discharge a week or so before they were due to be born whatever their weight at birth. Thus the 25 surviving babies born at 26–7 weeks' gestation (91 days before term) went home, on average, 84 days after delivery and seven days before they were due to be born (fig 2). Requirements for respiratory

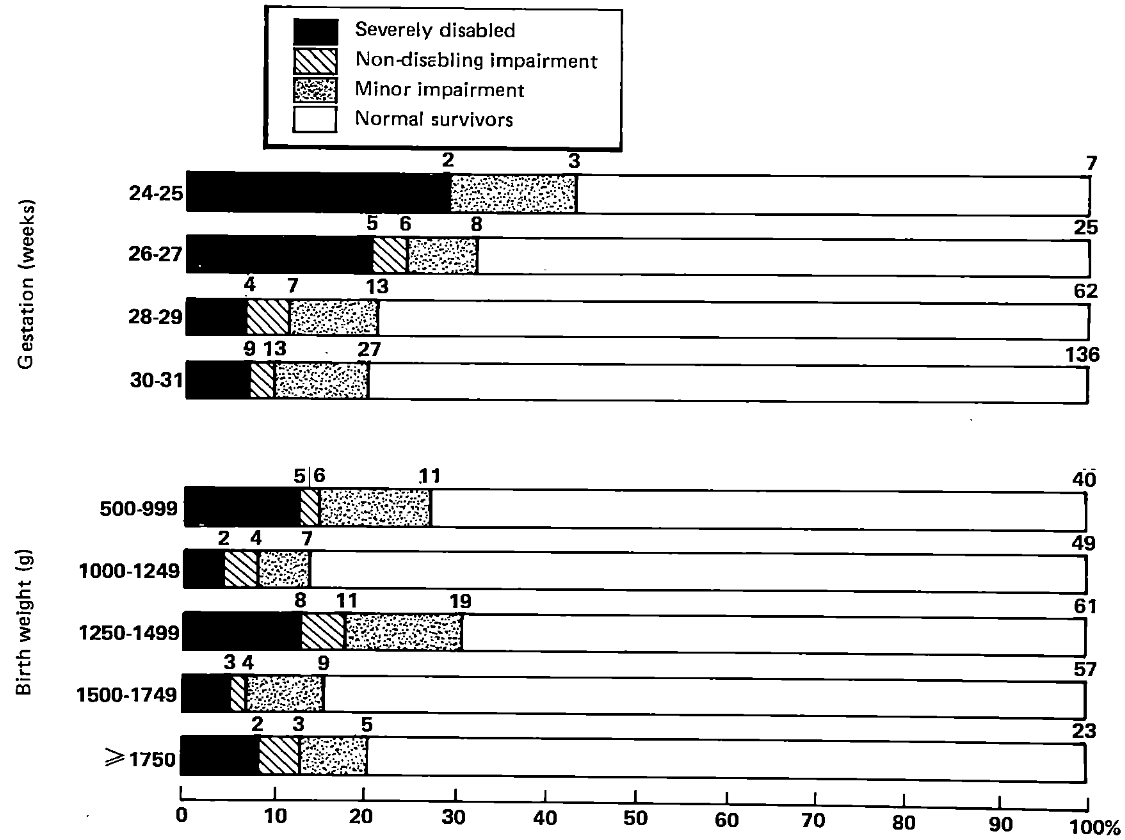

Fig 3 *Disability and non-disabling impairment at 2 years in babies of 24–31 weeks' gestation, showing the correlation with gestational age but the lack of correlation with birth weight.*

support and other high dependency care also varied inversely with gestation, with the disabled survivors at each gestation requiring marginally more care and support than the non-disabled survivors (fig 2).

Previous costing exercises have all been undertaken in large referral centres, and have been influenced by the biases caused by selective patient referral, have reflected medical practice in a single centre, and have sometimes only measured cost while in the referral centre rather than total cost to discharge. The broader approach adopted here provides a more accurate picture of the way in which the region's neonatal resources were used by the babies in this study. Such costing exercises, however, have their limitations. Many large unit costs (staff, hospital overheads, and so on) remain the same irrespective of the number of children cared for, or the amount of care invested in each patient. It will always seem cheaper to centralise the care of all babies requiring high dependency care to a few centres in each region to maintain a high cot occupancy, but such a calculation fails to allow for the need for district hospitals to maintain certain minimum neonatal staffing levels whether they undertake the care of babies requiring long term respiratory support or not. The opportunity cost of centralising high dependency care (the scope for redeploying existing staff and facilities in other ways) may be quite small. The case for centralising care depends on the argument that such a policy improves neonatal outcome.

### OTHER STUDIES

Direct comparison with other studies is impossible as all previous population based follow up studies have defined the group of children requiring follow up by birth weight, and used birth weight rather than gestational age to analyse the results obtained. Information was therefore collected about all the babies weighing 500–1500 g at birth who were born in the region in 1983 (whatever their gestational age). Of the children still alive 92% had no serious disability at the age of 2 years, a result that is broadly in line with earlier English community based studies from south east London, Mansfield, Wolverhampton, and Liverpool[16] of babies born between 1963 and 1981, although each of these studies defined disability in a slightly different way. Some classified epilepsy controlled by drugs, asymptomatic posthaemorrhagic hydrocephalus controlled by a ventriculoperitoneal shunt, and minor degrees of cerebral palsy that did not interfere with everyday activity, as evidence of 'disability', but these functional impairments (to use the terminology favoured by WHO[17]) often cause little disability. Nevertheless it seems clear from the available data that increased neonatal survival over the last 20 years has not been associated with any important change in the proportion of long term survivors with serious disabilities.

### PROGNOSIS

The present study highlights the poor prognosis that is associated with early neonatal fits, the increased incidence of disability in babies requiring more than two weeks of respiratory support (which may be partly due to a cross correlation with gestational age, fig 2) and the pronounced excess of male survivors with disabilities.

Outcome also seemed to be influenced by the obstetric factor that precipitated delivery. The chance of long term survival without disability in singleton babies of 24–31 weeks' gestation without malformations who were alive at the onset of labour or delivery was higher when delivery was precipitated by pre-eclampsia (73%) or antepartum haemorrhage (73%), than it was when spontaneous rupture of membranes before the onset of labour (60%), or spontaneous premature labour (52%), were the main obstetric factors. As the number of babies in each of these groups is comparatively small, the differences in prognosis may be a chance finding; minor differences in mean gestational age may be a further confounding factor. Nevertheless there is a clear need for further studies of this nature to see if such differences are consistently seen.

Nearly a fifth (19%) of the neonatal survivors after spontaneous premature labour were severely disabled, as were 13% of the neonatal survivors of abruption placentae and other severe antepartum haemorrhages. In contrast, only 3% of the neonatal survivors delivered because of pre-eclampsia, and 6% of the survivors whose delivery followed spontaneous rupture of membranes before labour were severely disabled. The mode of delivery had little discernible effect on mortality, or morbidity among survivors, once the obstetric factor precipitating delivery and the gestational age were taken into account.[1]

The main finding of the present study is that though disability in survivors is only poorly correlated with birth weight in babies born more than eight weeks early, it is strongly correlated with gestational age. Severe disability was seen in seven of the 32 long term survivors of 24–27 weeks' gestation (22%) and 13 of the 198 survivors of 28–31 weeks' gestation (7%) (fig 3). This is in line with the results of other community based studies that have shown that neonatal survival in such babies correlates much more closely with gestation than with birth weight.[18] The high incidence of disability in long term survivors of less than 28 weeks' gestation also confirms the findings from the few hospital based reports in which prognosis was assessed in terms of gestational age.[8] We believe these findings strengthen the case for using gestational age rather than birth weight as the yardstick by which to measure outcome in all future studies of perinatal mortality and morbidity, even though analyses by birth weight are, for the moment, the only way of comparing recently collected data with studies on babies born before 1980.

Obstetricians urgently need better and more detailed information on long term prognosis if they are to make informed decisions about the management of mothers who require delivery, or who threaten to deliver spontaneously, more than eight weeks before full term. Parents themselves also need such information if they are to be concerned in and consulted about management when problems of this nature arise. At this stage the obstetrician will know which is the primary factor complicating the pregnancy, and will have a good idea of the baby's gestational age, but will only have an imperfect assessment of the baby's weight.

These considerations point to the logic of reporting both short and long term outcome in terms of gestational age rather than birth weight. Resistance to such an idea has usually been based on a feeling that, though birth weight had been documented with some precision, information on gestation is necessarily imprecise. Though this is undoubtedly true, the need for precision can be exaggerated because children are usually subdivided into 100 g (or 250 g) birth weight groups for analytical and prognostic purposes. Furthermore, the advent of ultrasound scanning and of other techniques for dating pregnancies[19] have now increased the accuracy with which gestational age can be determined in early pregnancy. The case note review undertaken during the present study showed that serious errors often crept into the calculation and documentation of gestational age, but it also showed that the various primary criteria used to assess gestational age seldom gave estimates that differed by more than 10 days.

We conclude that although the routine documentation of gestational age at delivery is often unreliable at present this is not because precision is impossible, but because the need for precision is not recognised. As data continue to accumulate showing that gestational age rather than weight is the most powerful predictor of mortality and morbidity at birth in preterm babies, the importance of documenting gestation properly and the value of analysing long term outcome by gestational age, should become more generally recognised.

This study would not have been possible without the help that the region's paediatricians gave by retrospectively tracing the surviving children. We also owe a deep debt to the families of the children in the study. We are particularly grateful to Mrs B Gibson for her skill and commitment in gaining the cooperation and trust of the families, and in tracing those who had moved; it was her persistence and dedication that finally ensured that no child was lost to follow up. Dr Wariyar was a research registrar funded by the Regional Health Authority at the time of the study.

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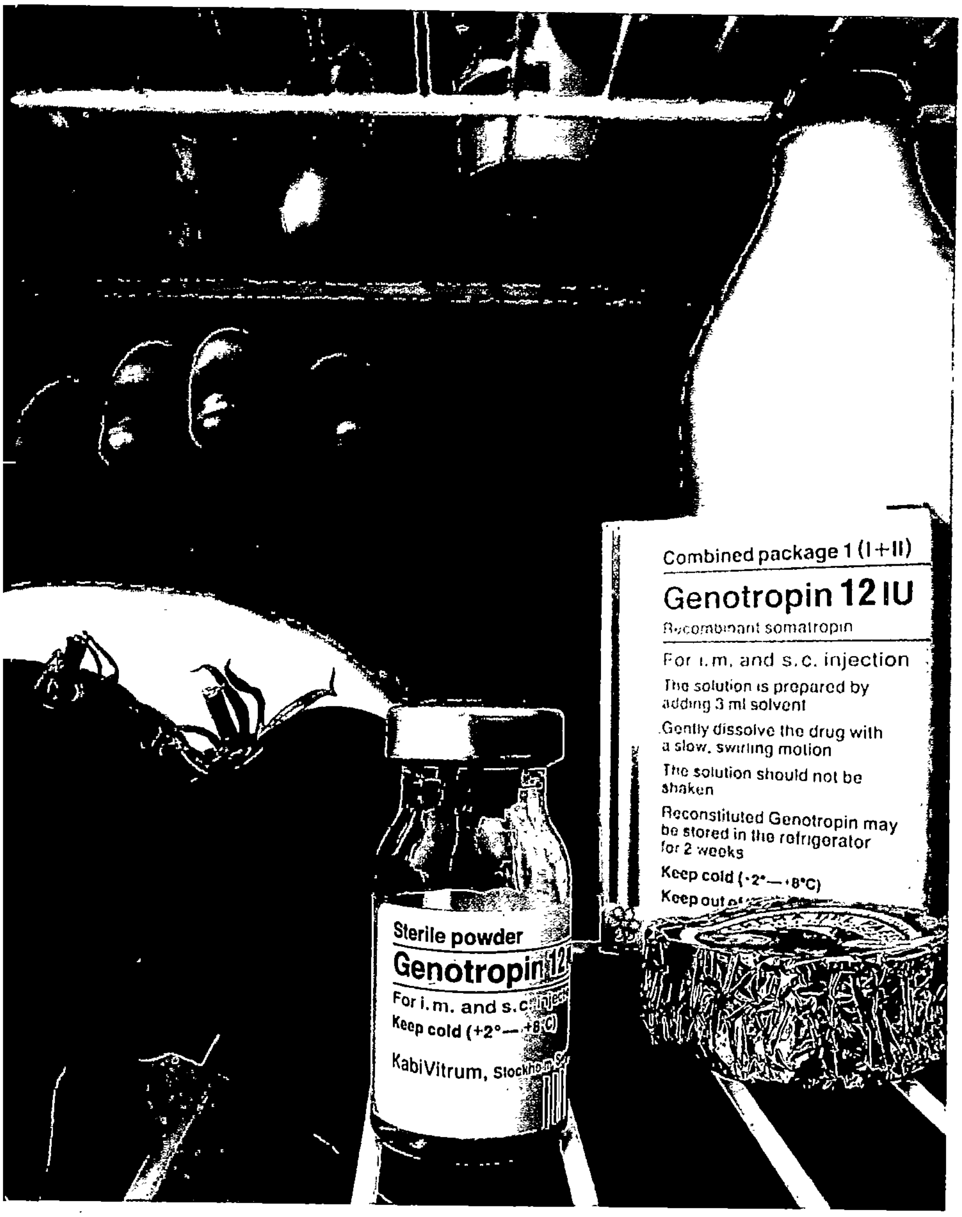
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# Rewarming preterm infants on a heated, water filled mattress

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SUMMARY Sixty low birthweight infants (1000–2000 g) admitted to a neonatal care unit in Turkey were studied. Those not requiring intensive care were randomly assigned for treatment either in a cot on a heated, water filled mattress kept at 37°C (n=28) or in air heated incubators with a mean air temperature of 35°C (n=32). On admission 53 (88·3%) of the infants had body temperatures between 30° and 36°C. There was good correlation between axillary and rectal temperatures in the infants while they were hypothermic. Normal temperatures were achieved within the first day and remained within this range during the subsequent days after admission in all the infants treated on the heated, water filled mattress, whereas they were not achieved until three days later in the incubator group. The neonatal mortality among those treated on the heated, water filled mattress was 21%, and among those treated in the incubator 34%. The heated, water filled mattress provides a good alternative to skin to skin contact with the mother, and to the use of a complex and expensive incubator for rapidly attaining and maintaining normal temperatures in the low birthweight newborn.

Hypothermia and cold injuries were among the main causes of neonatal death in the early 19th century.[1] The influence of thermal environment on the survival of premature newborn babies was clearly shown in the late 1950s.[2] Since then physiological studies have defined the physical environment for nursing newborn infants in incubators and have identified the critical environmental temperatures for the care of various groups of newborn infants.[3 4] Though the problem of neonatal hypothermia no longer exists in industrialised countries, there is evidence that it is still a serious threat to the lives of low birthweight infants in many developing countries, including those in the tropics.[5 6] The incidence of neonatal hypothermia is, however, unknown in many countries; this lack of information may be caused by unawareness of the problem because of the higher priorities given to other problems, to the shortage of funds in more general health programmes, or to the lack of specific low reading thermometers for recording low body temperatures.[7 8]

A prerequisite for treating low birthweight infants successfully, however, is to avoid hypothermia. Until now the use of air heated incubators, radiant heat sources, and the mother's body heat have been the only methods available. The first two methods are complex, expensive, and require a continuous supply of electricity; they are therefore not suitable for most developing countries. A cheap, safe, and effective compromise between a complex heat supply and the more primitive method of using the mother's skin is the heated, water filled mattress that was developed after recommendations from UNICEF and a commission in WHO.[9]

The main aim of the present study was to obtain information about the incidence of hypothermia among preterm infants in a neonatal care unit in a developing country. The second aim was to assess the effectiveness of rewarming low birthweight hypothermic infants on a heated, water filled mattress, by comparing them with infants nursed in an air heated incubator.

## Patients and methods

The study was undertaken in the neonatal care unit in the Department of Paediatrics at Capa Hospital, Istanbul, Turkey, from February 1986 to March 1987 with an interruption during the summer months from June to September. It included infants weighing between 1000 and 2000 g, and not older than 7 days, who had no serious malformations, seizures, or severe symptoms of respiratory distress requiring treatment with supplementary oxygen. Five heated, water filled mattresses were available at the neonatal care unit. Sixty infants who fulfilled the above criteria for the study were (on admission to the neonatal care unit) randomly assigned for treatment either on the heated, water filled mattress (n=28), or in the incubator (n=32).

Most of the babies (68%) came from the Capa Hospital delivery unit and were carried there by a parent, which took about five minutes. Sixteen babies (27%) were transported by car from other city delivery units located not more than 45 minutes away. Three babies (5%) arrived directly from their homes. During transportation the traditional swaddling was used with cotton sheets and a blanket. No transport incubator was available. The gestational age of the newborn infants was evaluated by Finnström's postnatal maturity method.[10]

The characteristics of the groups on admission are shown in the table. There were no significant differences between the groups in body weight or length, head or mid arm circumference, or gestational age.

The heated, water filled mattress was designed by Kanthal Medical Heating AB, in collaboration with paediatricians at the Huddinge Hospital. It consists of a polyvinyl chloride bag filled with 10 litres of water. The mattress is heated by a pad including a heating foil. It is covered with plastic and contains five built in thermistors. Two of the thermistors regulate the temperature, two are safety controls (to avoid overheating), and one records the temperature of the heated, water filled mattress on a digital display. The heating pad is supplied by 24 volts/AC with a maximum power of 50 watts. The temperature can be regulated in seven steps between 35°C and 38°C; overheating as well as underheating alarms are built in. When the electricity supply is interrupted the alarm rings.[9] The mattress is placed in the crib. Infants are dressed in a nappy, cotton shirt, and a dress. Infants weighing less than 1500 g wear a cotton cap as well. Each infant is placed on the mattress and covered with a blanket.

Table *Characteristics of infants on admission to the neonatal care unit. Values expressed as mean (SEM) except where otherwise stated*

| | *Infants treated on heated, water filled mattress (n=28)* | *Infants treated in incubator (n=32)* |
|---|---|---|
| Age (hours) | 33 (11·5) | 21 (6·7) |
| Weight (g) | 1504 (40) | 1517 (51) |
| Range | 1110–1900 | 1050–2000 |
| Length (cm) | 41·5 (0·5) | 41·3 (0·4) |
| Head circumference (cm) | 28·9 (0·3) | 28·5 (0·3) |
| Mid arm circumference (cm) | 7·6 (0·1) | 7·8 (0·2) |
| Gestational age (weeks) | 32 (0·5) | 32 (0·5) |
| Range | 28–35 | 27–36 |
| Rectal temperature on admission (°C) | 34·4 (0·3) | 34·2 (0·3) |
| Range | 31·0–36·3 | 30·6–37·0 |
| Axillary temperature on admission (°C) | 34·1 (0·2) | 33·9 (0·3) |
| Range | 30·7–35·9 | 30·2–36·6 |
| No (%) of infants who died | 6 (21) | 11 (34) |
| Mean age (days) | 7 | 4 |
| Rectal temperature on admission (°C) | 33·7 (0·3) | 33·4 (0·3) |

None of the differences is significant.

The incubators used in the neonatal care unit in Istanbul are standard models available on the ward (Draeger-6000 and Vickers-Medical Model 59). They are all single walled, manually controlled, and air heated. In the incubator the infant wears only a nappy. During the rewarming period after admission the mean (SEM) temperature setting of the heated, water filled mattress is 37 (0·1) to 38 (0·1)°C and that of the incubators is the highest temperature that the incubator can provide—35 (0·4)°C. After rewarming, the temperatures of the devices are set in accordance with the infant's rectal temperature and with the aim of obtaining a normal temperature of 36·5 to 37·5°C.[11]

The rectal temperature is measured 2 cm up the rectum by a 'low-reading' mercury thermometer designed for premature infants with a range between 27° and 41°C. The thermometers were tested by comparing them with a certified mercury thermometer which was placed in a water bath with a temperature between 30° and 40°C, and only those that were found to be accurate within 0·1°C were accepted. The axillary temperature was measured with an electronic thermometer of 0·1°C accuracy (Crafttemp)[12] at the same time as the rectal temperature. The axillary thermometer's disposable sensor was placed at the apex between the anterior and posterior margins of the axilla. The rectal and axillary temperatures were recorded on admission, and then twice daily between 7 and 8 am and again between 2 and 3 pm.

The air temperature of the incubator was recorded by the standard thermometer inside the incubators. The air temperature of the room was measured with a standard mercury thermometer. The water temperature of the heated, water filled mattress was recorded from the digital display of the unit. All measurements were performed by a nurse specially engaged for this study and the temperatures were measured twice a day.

All the infants were gavage fed either breast milk, or premature infant formula (Preaptamil, Milupa) if the mother could not produce enough breast milk. Body weight was measured on a standard baby scale sensitive to differences of 5 g; body length was measured in the supine position on a wooden scale, and head circumference and mid/upper arm circumference were measured with a standard tape. All measurements were made for every infant on admission to the neonatal care unit.

Mothers who were available during the first 24 hours after admission (26 of 60) were asked for their views about the mattress or incubator by a psychologist (DT), on the first day, and after one week of treatment.

The results are presented as mean (SEM) and range, the quantitative differences between the groups were calculated by the unpaired *t* test (one tail), and the frequency differences by $\chi^2$ analysis. For regression analysis the method of least squares was used. A p value of less than 0·05 was considered significant.

## Results

On admission most of the infants were hypothermic (table). Of 60 babies 53 (88%) had rectal temperatures below 36°C, and seven babies (12%) had rectal temperatures below 32°C (fig 1). Severe hypothermia (≤34°C) occurred regardless of place of birth (24% of babies born at Capa Hospital, and 63% of babies born in other delivery units) or season of the year (32% during December to February, and 39% during March to May). No significant correlation was found between the degree of hypothermia and the infants' age, birth weight, or gestational age.

When rectal and axillary temperatures were measured simultaneously good agreement was found between the two measurements (fig 2).

The results of rewarming the infants during the first three days after admission are shown in fig 3. There was a significant difference between the two treatment groups in the rectal temperatures. Infants treated on the heated, water filled mattresses were normothermic on the first day after admission and continued to have stable normal rectal temperatures on subsequent days. On the other hand hypothermia persisted in the infants treated in the air heated incubators and these infants did not become normothermic until the third day of treatment. The mean air temperature in the incubator was 33 (0·5)°C on the first day (n=32), 34·5 (0·3)°C on the second day (n=31), and 34·7 (0·4)°C on the third day (n=24). The mean room air temperature during the treatment of all babies was 24·5 (0·3)°C on the first day, 24·7 (0·2)°C on the second day, and 24·8 (0·3)°C on the third day.

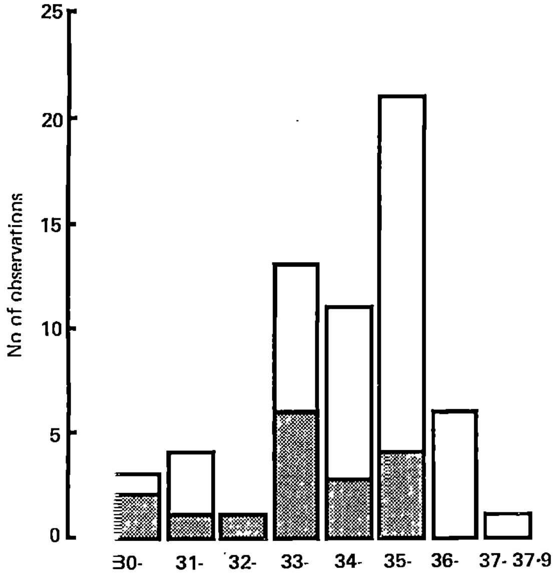

Fig 1 *Rectal temperature in 60 newborn low birthweight infants on admission to neonatal care unit. Shaded areas represent infants who died after admission.*

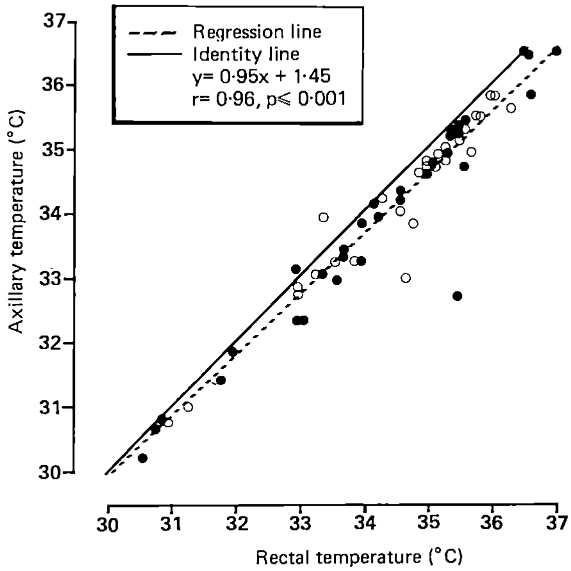

Fig 2 *Correlation between rectal temperature and axillary temperature in 60 infants on admission to the neonatal care unit. Open circles represent infants treated on heated, water filled mattresses; closed circles represent infants treated in incubators.*

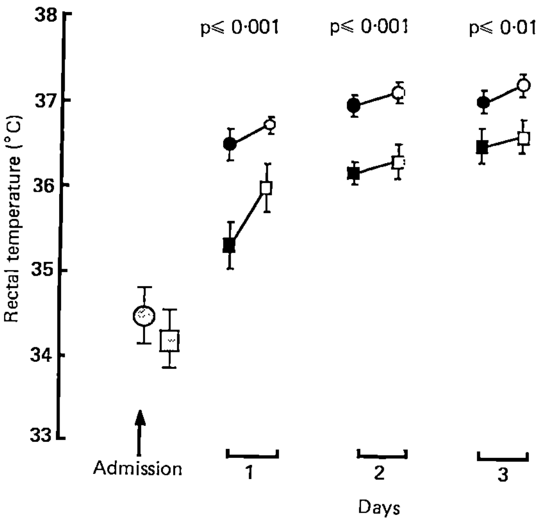

Fig 3 *Rewarming low birthweight infants during the first three days after admission to the neonatal care unit. Values are given as mean (SEM). Filled symbols indicate morning temperature, open symbols indicate afternoon temperature.* ■ □=*Treatment in incubator (n at day 1=32, at day 2=31, at day 3=24);* ● ○ *Treatment on heated, water filled mattress (n at day 1=28, at day 2=27, at day 3=25).*

A detailed analysis of the course of rewarming in four hypothermic infants (with rectal temperatures between 33°C and 34·2°C) on the heated, water filled mattress and one infant in the incubator is shown in fig 4. The rectal temperatures were recorded every 10 minutes. The temperature of the mattress was 37·5°C and of the incubator air 35°C. All four infants on the heated, water filled mattress achieved a rectal temperature of 36°C after 1·5 hours of rewarming; the infant in the incubator achieved a rectal temperature of 35·2°C after two hours.

Of 60 infants investigated during the study, 17 babies (28%) died after admission. In the heated, water filled mattress group, six of 28 infants (21%) died and in the incubator group 11 of 32 infants (34%) died. On admission, the mean rectal temperature of the infants who died was 33·7°C in the heated, water filled mattress group and 33·4°C in the incubator group (table). The main cause of neonatal death was probably infection, but no necropsies could be carried out. Breast feeding was encouraged on the ward. Among the 43 infants who survived the immediate neonatal period, 18 of 22 infants in the study group (82%), and 14 of 21 in the control group (71%) were being breast fed on discharge; this difference is not significant.

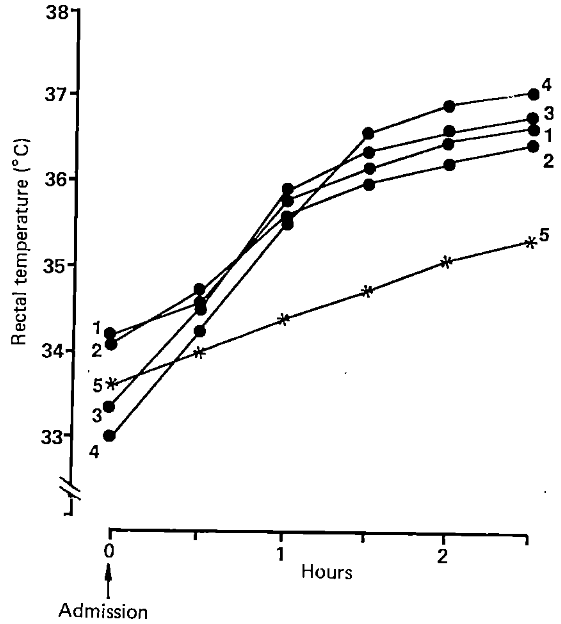

Fig 4 *Rewarming of five hypothermic infants. Cases 1–4 were rewarmed on the heated, water filled mattress and case 5 was rewarmed in the incubator. Body weight and admission age of case 1: 1100 g, 24 hours; case 2: 1270 g, not known; case 3: 1150 g, 2 hours; case 4: 1360 g, 17 hours; case 5: 1265 g, 4 hours.*

## Discussion

Only a few reports from developing countries on the incidence of hypothermia in low birthweight infants are available. Tafari from Ethiopia reported a high incidence of hypothermia (67%) in low birthweight infants on admission to the special care unit, and showed that in all birthweight categories there was a linear increase in neonatal mortality with falling body temperature.[7] No such report has come from Turkey.

The present study confirms that neonatal hypothermia in newborn low birthweight infants in developing countries is common. One reason why it is not recognised is that the lowest temperature that can be read on ordinary thermometers is 34°C and these thermometers are widely used. Infants with rectal temperatures below 34°C constituted 35% of all admitted infants to our study, and could not have been identified without the use of low reading thermometers.

There are good reasons to believe that the principal cause of the high incidence of hypothermia among preterm babies in our study is inappropriate handling of them immediately after birth. We studied 13 newborn babies born at full term after uncomplicated deliveries in the obstetric department at Capa Hospital in March 1987, and found that their rectal temperatures dropped to 35·2 (0·1)°C at 30 minutes after birth and rose to 35·5 (0·2)°C 2 hours later in a room temperature of 25 (0·3)°C. The reason for this heat loss was the absence of routines for drying the babies thoroughly and using the mother as an external heat source (I Sarman, G Can, unpublished observations). These findings confirm previous reports.[13] Most premature babies underwent similar procedures. The few available incubators in the nursery were old and ineffective for warming babies. By immediately drying and wrapping the newborn infant, and by using the mother's body heat in skin to skin contact as a heat source we believe it is possible to prevent neonatal hypothermia effectively.

Several investigations have shown close agreement between axillary and rectal temperatures in newborn, and especially in preterm, infants.[14 15] These measurements were made in normothermic babies but the results of our study in hypothermic preterm infants accord with these findings. Measurements of axillary temperature can therefore replace measurements of rectal temperature in such infants.

We have previously studied the thermal response of normothermic low birthweight infants in a prospective randomised controlled study by comparing the heated, water filled mattress treatment to treatment in an air heated incubator. No significant differences between the groups were found in minimal oxygen consumption, skin and rectal temperatures, and daily weight gain.[16] On the other hand the present investigation shows that the hypothermic infants were rewarmed more rapidly on the heated, water filled mattress than in the air heated incubator. One of the reasons for this may be the higher and more stable environmental temperature and the more effective heat conduction of the water in the heated, water filled mattress. When the electricity supply fails the high heat capacity of 10 litres of water keeps the water warm for several hours. The method of recording the incubator air temperature intermittently (twice daily in our study) is not enough for an analysis of the entire period of heating by the incubator. The presetting of an incubator temperature does not mean that the desired environmental temperature is kept constant in the air heated incubator during one day; the temperature immediately falls when the electricity supply is cut off. This happened almost every day during the present study, and it happens in most developing countries. The incubator needs to be operated by trained staff, and the portholes and doors must be completely closed to maintain a high air temperature. The neonatal care unit had only one full time nurse in the daytime. During the nights the one nurse available was on duty in at least one more unit. The responsibility for the care of the infants was therefore largely assumed by the mothers who were shown how to operate the warming equipment and supervise their infants. The mothers generally arrived late at the neonatal care unit after delivery because it took a long time to mobilise them and the hospital staff gave little help. The care of the babies whose mothers could not take care of them on the first days on the neonatal care unit was then primarily taken over by other mothers or relatives. This may further explain the incorrect changes in the incubator temperatures during the first days after admission that resulted in persistent hypothermia. It seems possible that the temperature of the equipment might be better regulated by allowing untrained mothers to feel the conductive heat by touching the warm water of a mattress instead of regulating the air temperature after reading a figure on a thermometer scale.

The plexiglass cover of the incubator hinders the mother's access to her child. A mother who delivers a premature infant suffers complete deprivation from the first day, and severe deprivation from then until the eighth week, if she can only see her child through a glass wall.[17] The care of a newborn infant on the heated, water filled mattress raises no such obstacle. Among the 26 mothers who were interviewed, the mothers of the infants treated on the heated, water filled mattress (14 of 15) greatly preferred the use of the mattress, which made it possible for them to touch their babies (I Sarman, G Can, D Toparlak, unpublished observations). Only one of 11 of the mothers of the incubator group preferred it. The heated, water filled mattress treatment probably strengthens early mother/infant bonding.

We suggest that every effort should be made to prevent hypothermia by early drying and by wrapping the newborn baby and giving it to the mother for close skin to skin contact. We believe that use of the heated, water filled mattress is more appropriate than the use of air heated incubators in rewarming babies when there are few—if any—qualified staff available to operate the more complicated air heated incubator.

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# Gall stones in Jamaican children with homozygous sickle cell disease

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SUMMARY Gall stones were detected by ultrasonography in 30 of 226 (13%) children with homozygous sickle cell disease aged 5–13 years participating in a cohort study from birth. Children with gall stones had significantly lower total haemoglobin and fetal haemoglobin and higher bilirubin concentrations, but further analysis showed that the apparent effects of haemoglobin and fetal haemoglobin concentration were secondary to their relationship with bilirubin concentrations. Abdominal pain crises were significantly associated with gall stones but both factors appeared to reflect an increased clinical severity and were probably not causally related. No patients had symptoms specific of gall stones and an association with abdominal pain crisis should not, of itself, be considered an indication for surgery.

Pigment gall stones are well recognised as a complication of sickle cell disease but previous data on their prevalence and pathologic significance have been collected from symptomatically ascertained patient populations. The present study reports the prevalence in a representative sample of patients with homozygous sickle cell disease followed up in a cohort study from birth. This has also allowed an assessment of risk factors for gall stone formation and an analysis of associated symptomatology.

## Subjects and methods

The children participated in a cohort study of sickle cell disease, which has been previously described.[1 2] During the screening of 100 000 consecutive deliveries,[3] 314 children with homozygous sickle cell disease were detected of whom six were lost to follow up immediately; 308 were admitted to the cohort study and followed up prospectively. Of these, 53 died, nine emigrated, and 246 (aged 5–13 years) continued to be observed at the time of the study.

From January to May 1987 all available children were examined by an experienced radiologist (JSD) using an ATL Ultramark IV with 3·0 mHz sector transducer. All studies were conducted in both transverse and longitudinal planes, with patients in a fasting state. Gall stones were diagnosed on the basis of echodense images within the gall bladder with either acoustic shadowing or gravitational change in position.

The haematological risk factors for gall stone formation were examined by comparing the means of steady state haematological indices in children with and without gall stones by Student's *t* test and by logistic regression analysis. These analyses were confined to steady state values over the age of 4 years because of rapid age related changes before this age.[2] All variables except total haemoglobin and direct bilirubin were transformed ($\log_{10}$ (variable+1)) to produce approximately normal distributions before analysis. These observations were also used to predict gall stone frequency according to age and total bilirubin concentration.

Clinical features were also compared in patients with and without gall stones. Pain crises were defined as pain severe enough to limit activity and to require narcotic analgesia and were divided into those affecting primarily the bones or joints (bone pain crisis) or the abdomen (abdominal pain crisis). Dactylitis was defined as painful, tender swelling over the small bones of the hand, foot, or digits with no evidence of local infection. Acute chest syndrome was characterised by fever, tachypnoea, and signs of pulmonary consolidation. Septicaemia referred to a clinically ill child with fever, positive blood culture, and no other focus of infection. The growth of children with and without gall stones was assessed by comparing mean heights and weights at the 5th and 9th birthdays.

The frequency of clinical events was assessed by deriving age specific incidence rates for pain crises, acute chest syndrome, and dactylitis in children with and without gall stones. As a few children with multiple events may distort these rates, a scoring system of 1–5 was used for bone pain crises and acute chest syndrome (representing 0, 1, 2–4, 5–9, 10 or more events) and of 1–4 for abdominal pain crises (representing 0, 1, 2, 3 or more events). These age specific incidence rates, derived for one year age bands, were compared between groups by analysis of variance. The relation of abdominal pain crisis with gall stones was reanalysed after controlling for bone pain crisis by examining this relation in groups matched for bone crisis frequency. This approach gives similar results to the stratified test for trend suggested by Mantel.[4]

## Results

Technically satisfactory ultrasound examinations were obtained in 226 of 246 (92%) of all available patients. Gall stones occurred in 30 (19 boys, 11 girls), increased with age, and reached a prevalence of 20% in those aged 11–13 years (table 1). Among those affected, the male:female ratio was 2·5:1 in the 5–7 year age group and 1·3:1 in children aged 11–13, but the overall sex difference was not significant ($\chi^2_1=0{\cdot}62$, $p=0{\cdot}42$).

Comparison of haematological indices showed that children with gall stones had significantly lower total haemoglobin and fetal haemoglobin and higher bilirubin concentrations (table 2). As these results may be influenced by mutual correlations between indices and the effects of age and sex, logistic regression analysis was used to assess the effect of each independently. Fitting all variables to two different models utilising either total bilirubin (model 1) or direct and indirect bilirubin (model 2), only total bilirubin ($p=0{\cdot}02$) and indirect bilirubin ($p=0{\cdot}04$) were significant indicating that after allowance for these factors, there was no additional effect of either haemoglobin or fetal haemoglobin. Results from the second model are shown in table 3. The predicted frequency of gall stones derived for different ages and bilirubin concentrations is shown in fig 1.

The scores for bone and abdominal pain crises (figs 2 and 3), and for acute chest syndrome, were consistently higher in children with gall stones, although only the difference for abdominal pain crisis reached significance ($F_{1,28}=4{\cdot}02$, $p=0{\cdot}05$). This observation could either imply a causal association between gall stones and abdominal pain crisis or that both factors reflect increased clinical severity. Analysis, repeated after controlling for bone pain crisis, showed that the relation of gall stones and abdominal pain crisis was no longer significant implying that their coincidence most likely reflected

Table 1 *Prevalence of gall stones according to age and sex*

| *Age group (years)* | *Boys* | | *Girls* | | *Total* | |
|---|---|---|---|---|---|---|
| | *No* | *No (%) gall stones* | *No* | *No (%) gall stones* | *No* | *No (%) gall stones* |
| 5–7 | 42 | 5 (12) | 37 | 2 (5) | 79 | 7 (9) |
| 8–10 | 44 | 6 (14) | 32 | 3 (9) | 76 | 9 (12) |
| 11–13 | 35 | 8 (23) | 36 | 6 (17) | 71 | 14 (20) |
| Total | 121 | 19 (16) | 105 | 11 (11) | 226 | 30 (13) |

Table 3 *Logistic regression analysis of some haematological and clinical features in patients with gall stones*

| *Variable* | *Slope* (logistic scale)* | *Significance* |
|---|---|---|
| Age | 0·09 | 0·32 |
| Sex (female) | −0·19 | 0·67 |
| Haemoglobin | −0·32 | 0·25 |
| Fetal haemoglobin† | −0·34 | 0·37 |
| Reticulocytes† | 0·05 | 0·96 |
| Direct bilirubin | 0·06 | 0·27 |
| Indirect bilirubin† | 0·79 | 0·04 |

*After allowance for all other variables.
†Transformed variables.

Table 2 *Haematology investigations in children with and without gall stones*

| *Variable* | *Gall stones present (n=30)* | | *Gall stones absent (n=196)* | | *t* | *p Value* |
|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | | |
| Fetal haemoglobin* | 0·72 (4·3) | 0·23 | 0·84 (5·9) | 0·28 | 2·15 | 0·03 |
| Haemoglobin (g/l) | 74 | 8·5 | 79 | 9·6 | 2·64 | 0·009 |
| Reticulocytes* | 1·09 (11) | 0·09 | 1·06 (10) | 0·11 | −1·30 | 0·19 |
| Direct bilirubin (μmol/l) | 17 | 3·4 | 15 | 4·0 | −2·16 | 0·03 |
| Indirect bilirubin* | 1·42 (25) | 0·24 | 1·26 (17) | 0·25 | −3·19 | 0·002 |
| Total bilirubin* | 1·64 (43) | 0·17 | 1·53 (33) | 0·17 | −3·46 | 0·001 |

*Indices expressed as values transformed by $\log_{10}$ (variable+1).
Figures in parentheses indicate means re-expressed in original units.

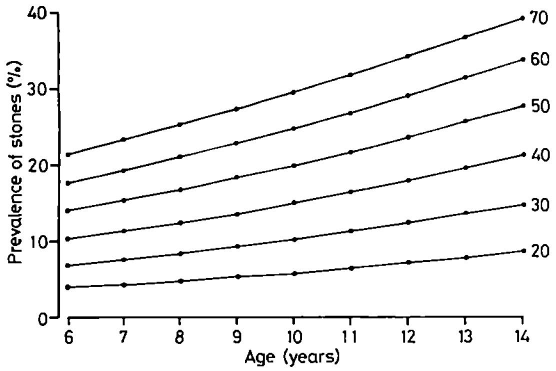

Fig 1 *Expected frequency of gall stones at different ages for different total bilirubin concentrations (µmol/l) derived from the observations.*

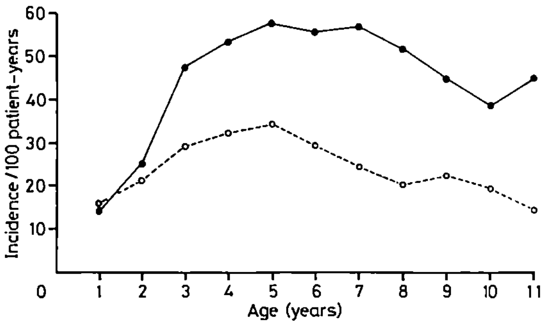

Fig 2 *Incidence of bone pain crises (derived as scores) in children with (●———●) and without (O — — — O) gall stones.*

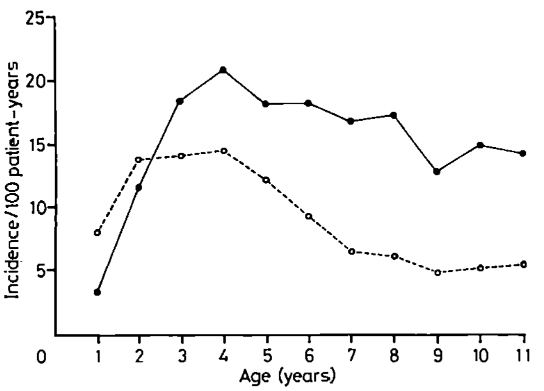

Fig 3 *Incidence of abdominal pain crises (derived as scores) in children with (●———●) and without (O — — — O) gall stones.*

an increased disease severity. No child had specific symptoms attributable to gall stones, and pain in the abdominal painful crisis was not localised to the right upper quadrant or epigastrium.

There were no differences in the incidence of septicaemia or dactylitis or in growth between the groups.

## Discussion

The prevalence of gall stones in this representative group of Jamaican children with homozygous sickle cell disease was 13%, considerably lower than the figures of 28–33% reported in age comparable groups in the United States.[5–8] In view of the genetic similarity of the two populations, it is likely that this difference represents the greater symptomatic selection in American series.

Information from other geographic areas is difficult to interpret. In Nigeria a low prevalence of cholelithiasis of 6% in patients under 15 years in one study[9] might have been attributed to the less sensitive diagnostic method of oral cholecystography, but later studies using ultrasonography reported similar low prevalences of 4·4% under 17 years[10] and 5% under 15 years.[11] It therefore seems likely that gall stones are truly infrequent in young Nigerian patients with homozygous sickle cell disease consistent with the infrequency of all gall stones in that population.[12] Since bilirubin concentrations in Nigerian patients with homozygous sickle cell disease are similar to those in Jamaica it must be concluded that pigment cholelithiasis is also influenced by other, possibly environmental, factors. In a Saudi Arabian study using oral cholecystography,[13] cholelithiasis was observed in only 8% of a population aged 10–64 years and did not occur in 26 patients under 17 years; this is consistent with the low bilirubin and mild haematological change characterising that population.

Apparent risk factors for gall stone formation in homozygous sickle cell disease in other studies have included low fetal haemoglobin concentration and high reticulocyte count[14] and high total[6 14] and indirect[14] bilirubin concentration. In the present study gall stones were associated with low total haemoglobin, low fetal haemoglobin, and high bilirubin concentrations. As both haemoglobin and fetal haemoglobin concentrations are inversely related to total bilirubin and as their contribution was lost on regression analysis it seems likely that their apparent effect was secondary to that of bilirubin concentrations.

The clinical significance of gall stones in homozygous sickle cell disease remains unclear. There is no doubt that complications such as acute cholecystitis or obstruction of the cystic or common bile duct may occur and may require surgical correction. The major question is the frequency of these complications and whether prophylactic cholecystectomy is justified. Gall stones affected 20% of a representative sample of Jamaican children with homozygous sickle cell disease aged 11–13 years, none of whom had symptoms clearly attributable to gall stones, although the significant association of gall stones with abdominal pain crisis might be inappropriately interpreted as an indication for cholecystectomy. Further analysis showed that such children were also more prone to bone pain crisis, and the disappearance of an association with abdominal pain crisis after correcting for bone pain frequency makes it likely that both gall stones and abdominal pain crises reflect clinical severity and are not causally related. Abdominal pain crisis in children with gall stones, therefore, should not be considered an indication for surgery unless there are features clearly referable to the right upper quadrant of the abdomen.

The arguments for prophylactic cholecystectomy of asymptomatic gall stones are based upon the assumption that these stones will become symptomatic.[5 15–20] This assumption was strengthened by a recent report from the United Kingdom indicating that pain typical of biliary colic occurred in 68% of adults with gall stones and that 21% developed acute cholecystitis.[20] It is difficult to reconcile these data with the Jamaican observations in which gall stones, although common, are relatively infrequently associated with typical symptoms. No symptoms have occurred in 30 cohort study children with gall stones—the oldest of whom are now approaching 15 years—and follow up of 32 adults known to have gall stones for 15 years showed only one patient developing specific symptoms during this period (DKH Webb and GR Serjeant, unpublished observations) and a current study of 31 patients with homozygous sickle cell disease over the age of 40 years has shown gall stones in 17 (55%) yet only two (6%) have had cholecystectomy for symptoms. A possible contributing factor to the apparent difference between the populations of the United Kingdom and Jamaica could be a greater symptomatic selection occurring in the group from the United Kingdom, and this is supported by the observation that 18 of 70 (26%) patients aged 16 years and above had already had cholecystectomies before the study in the United Kingdom.

The role of cholecystectomy for symptomatic gall stones is unquestioned but the Jamaican data do not support a policy of prophylactic cholecystectomy.

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# Life threatening illness and hospice care

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SUMMARY A retrospective study was undertaken of 25 families and their 26 ill children attending the first children's hospice in the United Kingdom. The study examined the family's perceptions of the care offered and the impact of chronic and life threatening illness.

Eighteen (72%) of the families felt they had been well supported by the hospice and valued the family like atmosphere, perceiving the staff to be friendly, approachable, and helpful. The actual nature of hospice care, in an environment with other terminally ill children, was, however, considered a drawback for a few families. A number of families still had unmet needs, notably appropriate child minding when away from the hospice.

The impact of chronic life threatening illness on the families was substantial. The parents (particularly the mothers), the index children, and their siblings all experienced much higher levels of psychological symptomatology than would have been expected from normal samples. While families felt greatly helped over symptom control, a proportion remained very worried about certain symptoms, particularly breathlessness, seizures, and pain. A high proportion of families were experiencing financial and employment difficulties as a result of their children's illnesses.

Since the early 1970s the adult hospice movement has gradually increased in size as a result of a growing awareness of the needs of terminally ill people and their families.[1] In the United States a comprehensive review of the work of the hospice movement (National Hospice Study) has been carried out,[2] while in Britain there have been reports of the work of individual hospices. The British studies have suggested that the quality of care offered by certain hospices is good. For example, Parkes compared the report of spouses of patients who died in a hospice with those of patients dying in a hospital ward.[3 4] The hospice group spouses spent more time at the bedside and reported less anxiety, and fewer felt that their spouses had suffered pain. The spouses of hospice patients also perceived the hospice ethos as 'family-like' and 'helpful'. None the less, despite the continued expansion of the adult hospice movement much of the care offered in hospices in Britain has not yet been evaluated.

In 1982 the first children's hospice in Britain, Helen House, was built in Oxford[5]; since then Martin House in Yorkshire has opened and others are planned. It seems essential at this stage in the development of children's hospices that the needs and problems of the families of children with life threatening illnesses are assessed and hospice care evaluated in a systematic manner.

This paper reports a retrospective study of Helen House which is the first phase of our evaluation of this hospice for children. The aims of this study were twofold: to assess the impact of chronic life threatening illness on the family and to examine the family's perception of the care offered by the hospice.

Helen House was opened in 1982 as a purpose built eight bedded unit and was funded by charitable subscription. It provides respite and terminal care on a 'home-away-from-home' basis for children suffering from chronic life threatening and terminal illnesses. It has space to accommodate families of children. Most children and families stay for up to two weeks at any one time but may return on a number of occasions, up to six or seven times per year depending on the need. The hospice attempts to provide a 'family-like' atmosphere. Half the staff have formal nursing qualifications. A full description of the hospice has been published elsewhere.[5]

## Subjects and methods

We aimed to study a series of families referred consecutively to Helen House, whose homes were within 50 miles of Oxford (a pragmatic decision taken before the study was commenced to facilitate home visits to the families). Twenty seven of the first 29 referrals were included in the study. Two families were excluded because the hospice staff felt it inappropriate for us to contact them at that time. Another two families were unable to take part: in one family the mother was terminally ill herself and the other family consisted of a single mother who was abusing illicit drugs, and whose child was in the final days of her illness. This left a study population of 25 families, 20 with surviving children ('surviving group'), and five whose children had already died ('bereaved group').

Written informed consent was obtained from all the families who were then seen at home for a single session of between two and three hours. We requested to see both parents, although our primary informant was normally the mother. The interview consisted of a semistructured questionnaire followed by a number of self report questionnaires that we asked the parents to complete in their own time and post back to us.

The semistructured questionnaire dealt with a number of issues: (1) background details and demographic data—including information about the family constellation—the family's medical history, and details of the child's illness. (2) Other services the family were receiving—including medical, educational, and social—in addition to the help they were receiving from Helen House. (3) The nature and extent of the child's symptoms. The parents were also asked to rate how worried they were about each symptom (scored according to Parkes[4]). (4) Family health, finances, employment difficulties, and coping strategies. (5) The extent to which the child's illness had limited the parents' social activities and the lives of siblings. (6) Perception of Helen House care—the extent to which the families felt they were supported and their needs catered for, especially those of the siblings. (7) Needs which they felt had not been catered for by any of the services, including Helen House.

Both parents were asked to complete self report questionnaires concerning: (a) their psychological health by the general health questionnaire,[6] (b) their marital adjustment by the dyadic adjustment scale.[7] and (c) their social adjustment by the social adjustment scale.[8] The mothers were asked to complete questionnaires (Rutter A2 scale[9]) concerning the emotional and behavioural state of the school aged 'intellectually intact' index children and their siblings. The mothers' return rate of the self report questionnaires was 100%. Two fathers did not return their general health and marital adjustment questionnaires.

### THE FAMILIES (TABLE 1)

There were 20 families with surviving children and five in which the index child had died. One of the families in the surviving group had two affected children. The mean age of the surviving children was 10·6 years, while the mean age at time of death of children in the bereaved group was 4·7 years. The mean length of illness of the surviving children was 7·6 years, and of the bereaved group was 2·7 years. Thus many of the children had suffered from their illnesses for most of their lives, the surviving group being older and having suffered longer from their illnesses.

The time scale of referrals to Helen House and our subsequent interviews varied substantially. The surviving group were referred to Helen House between six and 30 months before our interview and the bereaved group from between 12 and 30 months before our interview. The deaths within the bereaved group occurred between 11 and 23 months before the interview; no family was interviewed sooner than 11 months from the time of the child's death.

### DIAGNOSES (TABLE 2)

As can be seen from the table the children were suffering from a wide range of conditions with

Table 1 *Demographic data concerning the families, index children, and siblings*

| | *Families with surviving children* | *Bereaved families* |
|---|---|---|
| No of families | 20 | 5 |
| No of children | 21 | 5 |
| Mean (range) age of index children | 10·6 years<br>(4–17 years) | 4·7 years<br>(4 months–14 years) |
| Mean (range) length of illness | 7·6 years<br>(1½–15 years) | 2·7 years<br>(17 days–7 years) |
| Siblings: | | |
| Alive | 29 | 12 |
| Deceased | 4 | 1 |

Table 2 *The childrens' diagnoses*

| *Diagnosis* | *No of children* |
|---|---|
| Neurodegenerative disorder: | |
| With specified diagnosis | 5* |
| No specified diagnosis | 5 |
| Muscular dystrophy | 6* |
| Mucopolysaccharidosis | 3 |
| Cerebral neoplasm | 2** |
| Other | 5* |

*Denotes a child who has died.

neurodegenerative disorders and muscular dystrophy forming the largest groups.

SOURCE OF REFERRALS

Nine (36%) of the families referred themselves to Helen House (having heard about the hospice usually through the media and self help groups), six (24%) were referred by a paediatrician, and five (20%) by a social worker. The remainder originated from a variety of sources. None of the families were referred by a general practitioner. In subsequent years the source of referrals has changed and now includes children referred by general practitioners.

The amount of time spent by the children and their families at Helen House varied greatly. The surviving group had spent from between eight days to seven weeks over the previous 12 months (mean 24 days) at Helen House. The bereaved group spent from between three days to three months (mean 31 days) over the year before the child's death. Contact was maintained by letter or telephone between visits.

## Results

Statistical comparisons between the surviving group and the bereaved group were not considered appropriate. Not only were the bereaved group children significantly younger and suffering from illnesses of shorter duration, but the two groups were facing very different situations. The surviving group were coping with the ongoing illness of the child while the bereaved group were at various stages of dealing with the loss of the child.

FAMILY NEEDS, EXPECTATIONS, AND PERCEPTIONS OF HELEN HOUSE CARE

Each family had specific and individual reasons for seeking Helen House care, but a number of common themes emerged. Most common was the desire for care in a non-hospital environment with an emphasis on emotional support and time to talk in a relaxed and homely atmosphere. The second theme was the wish for medical care with emphasis on the relief of symptoms rather than on active intervention. Third was the need for respite care. One family, for example, had not had a day's break from their daughter since her birth 13 years previously (except for emergency admissions to hospital) until they came to Helen House. This family's plight was compounded by the fact that their daughter had manifested severe behavioural problems for many years.

HOSPICE HELP AND SUPPORT

Eighteen families (72%) felt very well supported by Helen House, the remaining seven only moderately so. The latter group's main reservations were about their own children seeing other ill and dying children. Many of the families commented on the opportunity to meet and receive support from other families at Helen House, and felt relieved to know that there was a place where their children could go when they as parents were ill, or a family crisis arose.

Many of the parents commended the fact that the entire family, including the siblings, were made to feel welcome at Helen House. They felt this contrasted with general hospital wards on which the family were often not readily received. The parents said the children often looked forward to the Helen House visits, and enjoyed being made to feel special as did the siblings.

The bereaved group felt particularly supported at the time of the child's death, especially those whose children died at Helen House. A variety of rituals surrounding the death were reported as being especially helpful—for example, bathing and laying out of the child after the death; the opportunity for the whole family to be with the child, and to spend time with the body in an unhurried manner. They also appreciated the flexibility of the ongoing support.

Many families felt reassured by the staff's evident experience with the children's illnesses, particularly the rare ones—for example, Batten's disease and the mucopolysaccharidoses. This gave them confidence in the staff's management of the complex combination of symptoms and deteriorating abilities that characterise many of these illnesses.

The parents were asked to rate on a scale of 1 to 5 (1, does not apply at all; 5, applies very much) their views of Helen House staff on a number of dimensions. Twenty three (92%) of the families saw the staff as very 'friendly', 'approachable', and 'helpful'; 12 (48%) rated the staff as very 'efficient'; and only five (20%) rated the staff as very 'busy'.

ADVERSITY FACTORS AND THE IMPACT OF ILLNESS ON THE FAMILY

It is important to note that there were five families who had already experienced the death of another previously ill child, as well as the one family who currently had more than one affected child.

*(1) Marital*

Among the surviving group three out of 20 were single parent families. Of the two parent families, five (30%) were experiencing substantial marital problems (using a score of less than 80, a conservative cut off on the dyadic adjustment scale). Of the five bereaved families, two had such marital problems.

*(2) Psychosocial functioning (parents)*

In the surviving group 45% of mothers and 27% of fathers had psychological difficulties (as indicated by scores of 12 or above on the general health questionnaire). These rates are both over 70% greater than those found in random community samples.[10] Notably 35% of the mothers and 17% of the fathers scored *very* highly (above 20) on the general health questionnaire. Furthermore 45% of mothers and 17% of fathers had been prescribed and had taken a course of tranquillisers over the preceding 12 months. These rates of tranquilliser use are approximately double those found in a community sample.[11] The parents were asked how they coped with stress and the extent to which they used alcohol and smoked cigarettes to cope with the child's illness (over and above their 'normal' intake). Of the mothers, 25% said they used alcohol to a moderate or great degree to help them cope, and 35% of fathers smoked moderately or heavily to help them cope.

Among the bereaved group, two mothers and one father were rated as having psychological difficulties on the general health questionnaire with one mother and one father scoring *very* highly. The general health questionnaire scores were generally lower in the bereaved group than in the survivor group.

*(3) Symptom worry*

Almost half the families (45%) of surviving children were very worried about at least one of their child's symptoms, particularly breathlessness and seizures (table 3). However, the extent of the worry did not necessarily relate to the severity of the child's symptoms. For example a mother of a child who was having up to 50 seizures a day, and was occasionally in status epilepticus, did not rate herself as being specially worried about the child's symptoms as she felt everything had been done to control them, and the child was not suffering any pain. Of the bereaved families three out of five recalled being very worried about at least one symptom. Most families spontaneously mentioned the care and attention that staff paid to symptom control and appreciated the experience of the staff and the very high priority placed on symptom relief.

Table 3 *Families' current worry over surviving child's symptoms*

| *Symptom* | *% Parents very worried** |
|---|---|
| Seizures | 25 |
| Breathlessness | 25 |
| Pain | 20 |
| Swallowing | 5 |

A total of 45% of families were *very* worried about at least one symptom.

*(4) Psychosocial functioning of children and siblings*

Of the 10 'intellectually intact' children, four (40%) were rated as having psychological difficulties on the Rutter A2 scale. These rates were approximately 75% greater than those found in normal children in primary care settings.[12] All of these problems were of an emotional nature, such as anxiety and unhappiness. Two fifths of all the school age siblings (n=20) were rated as having psychological difficulties: these children had either emotional, behavioural, or mixed emotional and behavioural problems.

Of the bereaved families, one set of parents felt so distressed about the sibling's problems that they felt unable to complete the questionnaire but they did report substantial problems in two siblings. Among the remaining four families there was a total of three school age siblings only; two of these had significant problems one of which had the highest score on the Rutter scales of any child in any group. His problems were both of a behavioural and emotional nature.

*(5) Financial*

A third of the surviving families felt they had made a substantial 'financial sacrifice' as a result of the child's illness; and one bereaved family reported likewise. Many of the families, however, pointed out that they did not see the term 'sacrifice' as appropriate but did acknowledge that having an ill child was very expensive. The sorts of expenses incurred were the cost of travelling and heating bills for keeping the house warm throughout at least nine months of the year. (Individual heating bills often exceeded £1000 per annum.)

*(6) Employment*

Many of the parents had experienced employment problems. Only a quarter of the surviving group mothers had any sort of employment; none worked full time and most worked only a few hours a week. Sixteen (64%) of the mothers had given up their jobs once the diagnosis had been made in order to look after the child. Among the bereaved group, three mothers worked part time and one had given up a job to look after the child. One father's business had gone bankrupt; he attributed this to the time he had spent looking after his child as well as the financial input needed to help care for the child.

### UNMET NEEDS

The most frequently mentioned concern was that of child minding facilities. Many parents (60%) said that the difficulties in obtaining child minders limited their lives to a substantial degree. It proved very difficult to secure a child minder for a child with a very serious illness particularly if a child suffered from epilepsy. A few families mentioned the need for local respite care. None felt the need for additional specialist medical care or intervention. A high proportion of families said they were concerned as to what would happen to their children if the parents themselves became ill or died before their children.

## Discussion

This study forms the initial phase of our evaluation of the first children's hospice in Britain and of the effect on the family of chronic life threatening and terminal illness in childhood. Until our prospective controlled study is completed in 1989 it will not be possible to assess the efficacy of Helen House compared with regular health service provisions in mitigating the impact on the family of life threatening and terminal illness in childhood. None the less certain noteworthy points arise from the present study. The findings suggest that the impact of these illnesses on the families studied is substantial. This manifested itself in a number of areas of psychosocial functioning. The parents experienced high levels of psychological difficulties with a number of families facing a great deal of marital stress. The index children had emotional difficulties and their siblings were experiencing emotional and behavioural problems at substantially higher levels than would be expected in a normal population. Furthermore a substantial proportion of families reported financial and employment problems that seemed to be significantly affecting their lives. Overall it seems that the mothers were carrying much of the burden of the emotional and employment problems. These problems, which are largely unremitting, are especially worrying in view of the length of the children's illnesses. While it is not possible to say whether this group of families is representative of all families who have children with life threatening illnesses, our findings are in keeping with other studies indicating that high levels of individual and family difficulties are very common in this situation.[13-16]

Most families felt that they were greatly helped by Helen House. The families were particularly reassured by the staff's experience and help with the symptoms and the disabilities inherent in these illnesses. Many pointed to the individualised approach to each child and family. Most valued the 'family-like' atmosphere with the option of 'whole family' involvement. This seemed to be especially important for the siblings who are so easily and perhaps inadvertently excluded by conventional hospitals. The actual nature of hospice care, however, in an environment with other terminally ill children, was a significant drawback for a few families.

These findings suggest that childrens' hospices offer a special style of care to families of children with life threatening illnesses. The hospice provides a warm friendly unhurried environment, unburdened by the rapid turnover and daily medical emergencies of the acute paediatric ward. This seems particularly appropriate for families suffering great strain, with children with degenerative conditions for which curative treatment is not appropriate. The hospice allows the whole family to be together instead of divided while focusing attention on symptom relief and helping the family cope with their worry over the symptoms. In some cases the hospice may have a special role around the time of death, providing the whole family with privacy, continuity of support, and ample time in situations when dying at home is not desired nor possible. Furthermore families facing the isolating long uphill struggle of many degenerative conditions are able to draw support from other families while attending the hospice.

While there might be certain special features of care which are offered by the hospice, certain aspects of the style and nature of care could be further enhanced in paediatric wards. For example, ward staff could focus their care not only on the child but on the entire family particularly the siblings. Simply making them all feel welcome and encouraging them to visit regularly is greatly appreciated. In addition, attention to symptom relief needs to be directed not only to reducing the severity of the symptoms, but to recognising and allaying the parent's anxieties and helping them to cope with the specific symptomatology. Furthermore, providing families with the opportunity to meet and draw support from each other may be helpful and while this may not always be possible on the ward, families may appreciate being put in touch with self help groups, for example the Muscular Dystrophy Society or the Mucopolysaccharidosis Society. Families may also be appreciative of short episodes of respite care. It should be emphasised that many of these children face years of a deteriorating illness and that hospice and hospital care are not mutually exclusive.

In conclusion this study points to certain issues that children's hospices should be able to address including: the provision of flexible care and support for the whole family (especially involving well siblings); continuity of support after the death of the child; help with anxiety over symptoms and their relief, and help with the physical problems of daily living. However, our findings also indicate that a number of the problems, particularly the financial and employment ones, go well beyond the remit of a hospice: these problems are not easily resolved but at least warrant recognition.[17]

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# Hypoxic-ischaemic encephalopathy after near miss sudden infant death syndrome

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SUMMARY Between 1982 and 1985, 14 infants aged 3–26 weeks presented with severe hypoxic episodes as a result of the 'near miss' sudden infant death syndrome (SIDS). They all had metabolic acidosis, cardiovascular instability, acute renal failure, ischaemic colitis, or acute neurological dysfunction. Investigation of the cause excluded infection and trauma, or a primary metabolic pulmonary, cardiac, or seizure disorder. Seven infants were deeply comatose on admission never regained consciousness, and died within 60 hours. A characteristic evolution of hypoxic-ischaemic encephalopathy not previously clearly described after near miss SIDS was seen in the seven who lived. Five of the seven were conscious within one hour of resuscitation and showed a striking interval of near normality before neurological deterioration that was characterised by status epilepticus, deep coma, and brain stem dysfunction from 36–96 hours after the event. A biphasic course was not apparent in the remaining two, each of whom was comatose on admission, though refractory seizures did develop. Computed tomograms of the brain more than a week after the event showed cortical infarction or cerebral atrophy. Six of the survivors, followed up from 16–55 months, have serious residual deficits including spastic quadriplegia, delayed development, cortical blindness, or infantile spasms.

'Near miss sudden infant death syndrome (SIDS) refers to the recognised clinical phenomenon of the rescue of an apparently healthy infant from a life threatening event. The infant is found limp, apparently unconscious, not breathing, pale or cyanotic, and requires stimulation or more vigorous resuscitation. Once specific toxic, metabolic, infectious, traumatic, and other identifiable causes for this life threatening event have been excluded, there remains a set of infants who for unknown reasons have experienced an inexplicable episode of near death.[1–3]

The vast number of publications on near miss SIDS suggests that infants either die or recover rapidly following such an event.[4 5] At most, subtle neurological abnormalities may occur.[6 7] Only a single report suggests that significant neurological dysfunction may occur.[8]

In order to clarify whether near miss SIDS is associated with considerable morbidity, a retrospective review was conducted of infants with a history suggestive of near miss SIDS and clinical evidence of hypoxic derangement of a number of organ systems, including the central nervous system, admitted to the intensive care unit of the Royal Alexandra Hospital for Children, Sydney.

## Patients and methods

The case histories of all infants admitted to the intensive care unit of The Royal Alexandra Hospital for Children, Sydney, for the period 1 June 1982 to 30 September 1985 were reviewed to identify those infants who had sustained a serious hypoxic injury as a result of near miss SIDS.

All subjects fulfilled the accepted criteria for the diagnosis of near miss SIDS. They had been found pale, cyanosed, limp or not breathing, and had required vigorous stimulation or cardiopulmonary resuscitation because death was thought to be imminent. In all infants, there was a lack of pathological events during pregnancy and delivery, including prematurity, and their neurological state seemed normal before the life threatening event. There was neither a history of seizures nor of fever.

Evidence of a hypoxic insult during admission consisted of metabolic acidosis (arterial pH 7·0 or less on presentation) or of cardiovascular instability (hypotension—that is, systolic blood pressure less than 40 mm Hg associated with poor peripheral perfusion), acute renal failure (absent or urinary output decreased to less than 1 ml/kg/hour, or serum creatinine concentration of over 100 μmol/l), ischaemic colitis (profuse watery, bloodstained diarrhoea with no other bacteriological, toxic, or surgical cause), or acute neurological dysfunction (deep coma or convulsions). Deep coma was diagnosed when the infant did not open his eyes (either spontaneously or in response to noise), made no sound, and made no purposeful response to localise or resist painful stimuli.

Infants were included in the study only if no obvious cause (sepsis, trauma, metabolic disorder, or primary pulmonary, abdominal, or cardiac abnormality) had been found for the life threatening event after extensive investigation during the hospital admission. Apart from detailed physical examination, this investigation included full blood count, estimations of the serum concentrations of electrolytes, ammonia, glucose, calcium, and magnesium, liver function tests, urinary amino acid screen, and organic acid profile by gas liquid chromatography. Cerebrospinal fluid was analysed, and viral and bacteriological cultures of blood, urine, stool, and cerebrospinal fluid were made. Chest radiography, electrocardiograms, and skeletal surveys were also carried out. Necropsies on those who died failed to establish a cause of death other than the primary hypoxic event.

The hospital records of those who lived were reviewed with particular reference to neurological state in the acute period. Serial electroencephalographic traces and cerebral computed tomograms were also studied. The neurodevelopmental outcome in the long term survivors, followed up clinically by the attending paediatrician, was recorded.

## Results

Fourteen infants from 3–26 weeks of age (mean 13 weeks) satisfied criteria for the diagnosis of a near miss SIDS event with a significant hypoxic insult. There were seven boys and seven girls. One child (case 1) has been previously reported and was found to have an incidental stage I neural crest tumour that resolved spontaneously without treatment. Urinary catecholamine excretion was normal.[9] As a comparison over the same period of time 35 other infants were admitted to the general hospital wards having had a near miss SIDS event that was not associated with hypoxic sequelae.

All infants were seen in hospital within 90 minutes of the life threatening event; six of the infants died within 24 hours. A further infant was withdrawn from life support systems after 60 hours because of brain death. Seven lived. All the children had previously been well and had not given cause for medical concern before the near miss SIDS event. Of those who lived, two had been slightly irritable and two had rhinorrhoea for a day or two before admission. Of those who died, two had been slightly irritable and one had had rhinorrhoea.

Of the seven who died, six were judged to have had cardiorespiratory arrest either at home by paramedical personnel, or in a hospital emergency department. Resuscitation consisted of intubation, artificial ventilation, and adrenaline given either intravenously or through the endotracheal tube. Estimated duration of arrest before resumption of cardiac output varied from 10–55 minutes. One other infant who died (case 13) presented with agonal gasping and unrecordable blood pressure. All these infants remained hypotensive and required volume expansion and inotropic support. Four developed signs of acute renal failure, and four ischaemic colitis.

After resuscitation at home all seven who lived had established spontaneous respirations by the time that they arrived in the hospital emergency department. Resuscitation had consisted of vigorous stimulation, mouth to mouth resuscitation or cardiac massage. One infant required resuscitation with a bag and mask (case 7). Three of these infants required intravenous colloid and inotropic support to maintain adequate cardiac output. Three developed ischaemic colitis, and two acute renal failure (one of whom required peritoneal dialysis).

Table 1 shows the evidence of hypoxic derangement during admission in the two groups. Metabolic acidosis on presentation, continued cardiovascular instability, acute renal failure, or ischaemic colitis occurred more often among those who died. In two infants (cases 2 and 4) acute neurological dysfunction was the only evidence of an hypoxic injury. Liver function tests showed a mild increase in the transaminase activity in two cases (cases 1 and 6). Three infants (cases 1, 3, and 4) developed hyponatraemia secondary to inappropriate antidiuretic hormone secretion during admission.

### ACUTE NEUROLOGICAL COURSE

All seven who died were in deep coma at their initial presentation and remained so until the time of death. In all but one the pupils did not react to light at initial presentation. Three patients (cases 8, 10, and 13) developed seizures before death.

Two distinct patterns of neurological dysfunction were seen in the seven survivors. All had normal pupillary reactions at the initial assessment; details of their neurological course and outcome are shown in table 2.

Five of the infants (cases 1–5) showed a biphasic evolution of neurologic dysfunction characterised by

Table 1 *Clinical signs of hypoxic insult*

| *Case No* | *Sex* | *Age (weeks)* | *Initial pH ≤7·0* | *Cardiovascular instability* | *Acute renal failure* | *Ischaemic colitis* |
|---|---|---|---|---|---|---|
| **Those who lived:** | | | | | | |
| 1 | Female | 7 | Not measured | No | No | Yes |
| 2 | Male | 17 | No | Yes | No | No |
| 3 | Male | 26 | No | No | No | No |
| 4 | Female | 12 | Not measured | No | No | Yes |
| 5 | Male | 13 | Not measured | No | No | No |
| 6 | Male | 4 | Not measured | No | Yes | Yes |
| 7 | Female | 8 | Yes | Yes | Yes | No |
| **Those who died:** | | | | | | |
| 8 | Female | 9 | Yes | Yes | Yes | No |
| 9 | Female | 3 | Yes | Yes | Yes | Yes |
| 10 | Female | 11 | Yes | Yes | No | Yes |
| 11 | Male | 14 | Yes | Yes | Yes | Yes |
| 12 | Male | 16 | Yes | Yes | Yes | Yes |
| 13 | Female | 11 | No | Yes | No | No |
| 14 | Male | 20 | Not measured | Yes | No | No |

Table 2 *Details of neurological course and outcome of those who lived*

| *Case No* | *Neurological state on admission* | *Onset of seizures (hours after event)* | *Onset of deep coma (hours after event)* | *Duration of of deep coma (hours)* | *Outcome* |
|---|---|---|---|---|---|
| 1 | Irritable, did not follow light, abnormal tone, reflexes | 2 | 96 | 48 | Spastic quadriplegia, severe cortical blindness, infantile spasms |
| 2 | Awake, alert, active, vision fixed momentarily | 36 | 48 | 4 | Moderate developmental delay, moderate cortical blindness, infantile spasms |
| 3 | Alert, active, vision fixed momentarily | 51 | 96 | 60 | Cortical blindness on discharge from hospital |
| 4 | Alert at times, occasionally lethargic | 14 | 72 | 60 | Moderate developmental delay, moderate cortical blindness, infantile spasms |
| 5 | Lethargic, few spontaneous movements | 3 | 72 | 120 | Spastic quadriplegia, mild cortical blindness, infantile spasms |
| 6 | Slow withdrawal to pain | 5 | At presentation | 120 | Spastic quadriplegia, severe cortical blindness |
| 7 | Flaccid, no response to painful stimuli | 42 | At presentation | 96 | Mild developmental delay, severe cortical blindness, infantile spasms |

an initial period of near normality and subsequent neurological deterioration. These five infants were conscious and rouseable within one hour of resuscitation. They were awake, alert and active, or irritable or lethargic with only minor abnormalities of tone and deep tendon reflexes. In three cases there were concerns about their ability to fix their gaze. This striking interval of near normality continued until the onset of seizures from 2–51 hours (mean 21 hours) after the event. In one patient (case 1) isolated myoclonic jerks, evident at initial presentation, did not recur until 18 hours after the event. The seizures (initially tonic or multifocal and clonic) increased in frequency and duration with eventual secondary generalisation from 28–72 hours (mean 51 hours) after the event. Status epilepticus, defined as a generalised convulsion which lasted more than 30 minutes or as serial convulsions between which there was no return of consciousness, occurred in all five.[10] Two patients in this group required an infusion of thiopentone to control the seizures. Associated with increasing severity of the convulsions there was overall deterioration in the infants' neurological condition, with progression to deep coma from 48–96 hours after the event. Deep coma, as defined previously, persisted from 4–120 hours (mean 58 hours). Signs of brain stem dysfunction—that is, no oculocephalic responses (cases 3 and 4), pupillary inequality (case 1), and divergent eyes (case 5)—occurred in four of the patients in association with deep coma. The fontanelle was bulging in four.

The other two survivors (cases 6 and 7) were deeply comatose on admission. A biphasic course was not apparent though refractory seizures did develop. One of these patients (case 7) also required an infusion of thiopentone.

Cranial computed tomograms were obtained in all except one of the patients (case 6). Early scans (obtained within eight days of the life threatening event) were normal (cases 2 and 4), or showed focal (case 3), or generalised (case 1) hypodensity, suggestive of cerebral oedema. Cranial ultrasound in this last case showed increased density in the subarachnoid space suggestive of blood, but this was not confirmed on computed tomography. Cranial ultrasound in case 6 showed no abnormality. Computed tomograms obtained after the first eight days were normal in one case (case 2), or showed changes of cerebral atrophy in one patient (case 3), and frontal, temporal, or occipital low attenuation areas consistent with watershed infarction in three (cases 4, 5, and 7).

Ictal activity on an abnormal background rhythm of low amplitude slow waves was seen in five of the six patients in whom electroencephalographic traces were obtained within one week of the life threatening event. This activity consisted of either rhythmic spike and slow wave resembling paroxysmal lateralising epileptiform discharges in three cases (cases 2, 6, and 7), or rhythmic spikes in two (cases 4 and 5). The discharges characteristically arose unilaterally in alternate hemispheres, or occasionally synchronously in both. The one patient in whom ictal activity was not seen (case 3) was receiving an infusion of thiopentone at the time of the record. Electroencephalographic records after the first week showed persistence of the abnormal background rhythm with the disappearance of ictal activity.

### OUTCOME

Six of the seven infants (cases 1, 2, 4, 5, 6, and 7) have been followed up for periods of one year four months to four years seven months (mean two years eight months) and they all show evidence of serious handicap. One child (case 3) was unfortunately lost to follow up, but was said to be developmentally normal one year after the event when reviewed by his local doctor.

Three of the survivors (cases 1, 5, and 6) are severely handicapped by spastic quadriplegia and live in institutions. The remaining three (cases 2, 4, and 7) are mildly or moderately developmentally delayed as assessed with the Reynell-Zinkin Developmental scales for young visually handicapped children and the Maxfield-Bucholz scale of social maturity.

All survivors are cortically blind. Three of them (cases 1, 6, and 7) are severely impaired and have light perception only. One (case 5) can distinguish large objects at one metre, and two (cases 2 and 4) can do so at three metres. Visual function in these two is characterised by visual inattention and variability. Case 3 was cortically blind at discharge from hospital. He was said to have normal vision one year after the event.

Five infants developed infantile spasms with electroencephalographic changes of true or modified hypsarrhythmia.

## Discussion

The exact association between near miss SIDS and SIDS is unclear. Most series emphasise a possible overlap between the two (similar age distribution and more male and preterm infants and siblings of SIDS victims than in the general population). Babies referred as 'near miss' infants probably are, as a group, at increased risk for sudden death.[1–4 11–13]

Near miss SIDS may represent a pathophysiological disorder characterised by prolonged central or mixed apnoea, the end result of which may be sudden death.[13 14] It has been suggested that a child either dies from SIDS, or recovers from near miss SIDS after a life threatening apnoea, and that this recovery is complete.[4 5] The literature does not address the possibility that recovery from near miss SIDS is not always an 'all or nothing' event. Significant hypoxic sequelae are not reported.

This study identifies a selected group of infants who were resuscitated from a 'near miss' event and who also showed clinical evidence of hypoxic derangement of at least one, and often many, organ systems. Necropsies showed findings consistent with a diagnosis of SIDS. Careful clinical and laboratory investigations in the surviving infants excluded specific toxic, metabolic, infective, and other causes. All the infants were neurologically normal before the event. The infants did not fulfil the criteria for the diagnosis of the syndrome of haemorrhagic shock and encephalopathy which, in addition to encephalopathy and convulsions, is also characterised by a high fever, severe hepatic dysfunction, and a haemorrhagic diathesis.[15 16]

Mortality in this selected group was high and the survivors developed serious neurological complications. In most of the survivors the acute neurological course started with a normal period, and coma and convulsions developed later. The long term outlook was poor, with cortical blindness, infantile spasms, and varying degrees of developmental delay.

The findings presented here contrast with those that suggest that infants either die or recover rapidly after a 'near miss' event. By selecting a group with hypoxic derangement, many infants who do recover rapidly have been excluded. It remains surprising, however, that reports of significant neurological deficits after near miss SIDS are infrequent. Aubourg *et al* described 12 infants with status epilepticus in eight of whom a history of an unrecognised life threatening event 36 hours to four days before the onset of epilepsy, was retrospectively obtained.[8] These infants shared many features with the babies reported here including an interval of near normality, similar electroencephalographic features, and a high frequency of handicap including cortical blindness, a well known manifestation of hypoxic insult.[17]

Interestingly, Kelly *et al* described a number of infants who required bag and mask resuscitation from a near miss episode. These infants developed transient lethargy, poor fixation on objects, hyperreflexia, and clonus.[4] In addition the same group reported that some infants who had repeated, severe near miss episodes requiring resuscitation or vigorous stimulation later developed a seizure disorder.[11]

The poor prognosis of this selected group of infants is not surprising. Deep coma for even a few hours may be associated with poor neurological recovery in older children.[18] Fixed, dilated pupils, the continued need for cardiopulmonary resuscitation, and severe metabolic derangement at initial assessment all predict a poor prognosis in studies of near drowning.[19] [20] Snyder *et al,* however, reported that normal consciousness after an anoxaemic episode and before the onset of seizures is associated with a comparatively favourable outcome.[21] [22] It is apparent that in the babies described here the period of near normality after the hypoxic-ischaemic insult was not associated with a good prognosis.

As hypoxic-ischaemic encephalopathy after near miss SIDS has not previously been clearly delineated, the most interesting aspect of this study is the clearly biphasic course of five of the survivors. The interval of near normality before the secondary neurological deterioration is similar in many ways to the early period of hyperalertness that typically gives way to increasing stupor and seizures in severe perinatal hypoxic-ischaemic encephalopathy.[23]

The phenomenon of delayed neurological deterioration after anoxia, first described by Plum and Posner, should be clearly distinguished from the delayed onset of seizures and coma in the infants described in this report.[24] [25] The former condition predominantly affects white matter, is thought to be due to demyelination, usually occurs from two to eight days after the anoxic event, and is characterised by pyramidal and extrapyramidal signs and symptoms without seizures. The condition reported in this paper probably reflects acute hypoxic-ischaemic encephalopathy, a triad of multifocal necrosis, vasogenic oedema, and raised intracranial pressure affecting primarily the grey matter.[26]

The results of recent experimental work have suggested that the clinical characteristics of acute hypoxaemic encephalopathy—that is, the hyperalert state and the seizure activity, may relate to hyperactivity of excitatory synapses that are highly concentrated in those regions of the developing brain vulnerable to hypoxic-ischaemic damage. Excessive release of neurotransmitters (particularly glutamate) triggers a cascade of biochemical reactions and potentially lethal ionic shifts with eventual neuronal death taking place over hours or days.[27]

Specific treatment, including glutamate antagonists, may soon become available so that this cascade of biochemical events can be interrupted. Flunarizine hydrochloride, a commercially available calcium channel blocker, has been shown to block the effects of brain perinatal hypoxaemia-ischaemia in an in vivo model and offers exciting prospects for the reduction of the serious consequences of hypoxaemic-ischaemic encephalopathy.[28] It is possible that the early use of anticonvulsants may prevent refractory seizures that coincide with deteriorations in mental state.

Before such treatments are available, knowledge of the present poor prognosis of this unfortunate group of infants may be of value as a guide to acute treatment regimens, in parental counselling, and in the anticipation of long term rehabilitation needs.

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# Thyroid function in survivors of cancer

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SUMMARY Thyroid function was assessed in three selected groups of children who had survived cancer. Children in group 1 had received radiotherapy to the thyroid area, group 2 had radiotherapy to the thyroid area and adjuvant chemotherapy, and group 3 had chemotherapy with or without radiotherapy away from the thyroid area. There were 75 survivors and 63 (40 boys 23 girls) were available for study. Eighteen (29%) were found to have thyroid dysfunction, and these included all those who had had lymphangiograms or received a radiation dose greater than 40 Gy to the thyroid area. Only nine of the 18 children were already known to have thyroid dysfunction, and only 15 of 44 children who had had irradiation to the thyroid area had had their thyroid function examined.

This study shows that children who have received radiotherapy to the thyroid area should have their thyroid function assessed regularly. Chemotherapy does not appear to be a risk factor but longer follow up of these children is necessary.

The survival rates for childhood cancer have improved consistently over the last two decades and many children are now cured.[1] This improved prognosis follows intensive treatment with cyclical chemotherapy and high dose irradiation, but unfortunately this can also cause a number of side effects including thyroid dysfunction.[2–6]

This study reports the prevalence of thyroid dysfunction among the survivors of selected childhood cancers in the South West region of England. To evaluate its aetiology we have included children who had received various treatment schedules involving chemotherapy or radiotherapy, either alone or in combination.

## Patients and methods

The children were the survivors of selected childhood cancer treated in the South West region of England. The population of this region is approximately 3 million and about 70 new patients with cancer are treated annually at the Bristol Children's Hospital Regional Oncology Centre.

Three groups were included in the study. Group 1 had received radiation fields that included the thyroid gland, but had not been treated with any chemotherapy; group 2 had received chemotherapy in addition to radiation involving the thyroid gland; and group 3 had received chemotherapy but any radiation field excluded the thyroid area.

There were 75 survivors of the cancers selected for this study but only 63 children (40 boys and 23 girls) were included as four had left the area and in eight information on thyroid function could not be obtained.

Clinical data were extracted from the notes. Thyroid function was assessed by measuring serum thyroxine and thyroid stimulating hormone concentrations. Thyroxine was measured by radioimmunoassay and thyroid stimulating hormone by specific double antibody immunoradiometric assay. The normal range in our laboratory for thyroxine concentration is 65–170 nmol/l and for thyroid stimulating hormone <6 mU/l. Thyroid dysfunction was defined as either compensated hypothyroidism (raised thyroid stimulating hormone, normal thyroxine), primary hypothyroidism (raised thyroid stimulating hormone, low thyroxine), or secondary hypothyroidism (normal thyroid stimulating hormone, low thyroxine).

Most patients were treated with a cobalt machine, although a few were treated using a linear accelerator and some by electrons. Estimates of the irradiation dose to the thyroid gland were determined by reviewing the treatment plans and dose prescriptions. The absorbed dose outside the radiation beam was estimated using data from measurements of total scattered and leakage radiation in a water phantom.

## Results

Eighteen (29%) children had evidence of thyroid dysfunction: 10 (16%) with compensated hypothyroidism, and eight (13%) with primary hypothyroidism. None had secondary hypothyroidism. At the time of the study only nine of the 18 children were recognised as having thyroid dysfunction. The clinical data are listed in table 1.

Only 15 of 44 children at risk of developing thyroid dysfunction after radiotherapy to the thyroid area or lymphangiography, or both, had had their thyroid function assessed. Their mean age of follow up was 4·73 years (range 1·2–14·8).

RADIOTHERAPY GROUP

There were 11 children in this group: eight with medulloblastoma and three with Hodgkin's disease. The irradiation dose to the thyroid area varied from 30–40 Gy. Five (46%) children had thyroid dysfunction (table 1). There was no apparent difference in the age at diagnosis, irradiation dose, fractions of dose, or follow up between those who developed thyroid dysfunction compared with those with normal thyroid function.

CHEMOTHERAPY GROUP

There were 20 children in this group. They included four children with Hodgkin's disease, three with rhabdomyosarcomas, seven with Ewing's tumours, three with osteosarcomas, and three with acute myeloid leukaemia. The chemotherapy used included a combination of at least three of the following cytotoxic drugs: vincristine, cyclophosphamide, doxorubicin, lomustine, actinomycin D, cytarabine, etoposide, ifosfamide, vinblastine, cisplatin, carboplatin, procarbazine, teniposide, dacarbazine, hydroxyurea, epirubicin, chlorambucil, mustine, daunorubicin, prednisolone, and methotrexate. All these children had normal thyroid function apart from one with Hodgkin's disease who had had a diagnostic lymphangiogram (table 1).

CHEMOTHERAPY AND RADIOTHERAPY GROUP

There were 32 children in this group. They included six children with medulloblastoma, three with cerebral tumours, six with rhabdomyosarcomas, six with Hodgkin's disease, three with acute myeloid, and eight with acute lymphoblastic leukaemia with central nervous system relapse resulting in thyroid radiation. The irradiation dose to the thyroid area ranged from 4 to 56 Gy. The chemotherapy used varied from a single agent to intensive combination chemotherapy. Twelve (38%) children had thyroid dysfunction and 11 of them had received an irradiation dose to the thyroid area in excess of 20 Gy, the remaining child had received total body irradiation (11 Gy) (table 1).

DIAGNOSIS, TREATMENT AND THYROID FUNCTION (TABLE 2)

*(A) Medulloblastoma patients (n=14)*

All these children had similar irradiation dose involving the thyroid area averaging 35 Gy (range

Table 1 *Clinical data on 63 survivors of childhood cancer*

| *Treatment* | *No of patients* | *Mean (range) age at diagnosis (years)* | *Mean (range) follow up (years)* | *No with thyroid dysfunction* |
|---|---|---|---|---|
| Radiotherapy | 11 | 9·0 (3·0–14·7) | 5·5 (2·9–11·2) | 5 |
| Chemotherapy | 20 | 6·1 (0·2–14·0) | 3·8 (0·8–11·9) | 1 |
| Radiotherapy and chemotherapy | 32 | 8·0 (0·2–13·2) | 7·0 (1·4–14·8) | 12 |
| Whole group | 63 | 7·5 (0·2–14·7) | 5·6 (0·8–14·8) | 18 |

Table 2 *Clinical data on tumour type and thyroid function in 63 patients*

| *Diagnosis* | *No of patients* | *Mean (range) age at diagnosis (years)* | *Mean (range) follow up (years)* | *Thyroid dysfunction* | *Raised thyroid stimulating hormone/ normal thyroxine* | *Raised thyroid stimulating hormone/ low thyroxine* |
|---|---|---|---|---|---|---|
| Medulloblastoma | 14 | 8·0 (3·2–13·3) | 6·2 (2·9–11·6) | 5 | 3 | 2 |
| Hodgkin's disease | 13 | 9·2 (3·4–13·3) | 5·3 (1·4–10·5) | 6 | 3 | 3 |
| Bone tumour | 10 | 10·2 (6·3–14·0) | 3·3 (0·8–7·7) | 0 | 0 | 0 |
| Rhabdomyosarcoma | 9 | 7·6 (1·0–13·0) | 5·9 (1·0–11·9) | 3 | 0 | 3 |
| Acute lymphoblastic leukaemia | 8 | 5·3 (1·2–10·9) | 7·3 (2·3–14·8) | 2 | 2 | 0 |
| Acute myeloid leukaemia | 6 | 5·9 (0·2–12·2) | 3·5 (0·8–6·9) | 2 | 2 | 0 |
| Brain tumour | 3 | 1·9 (1·0–3·7) | 5·6 (1·4–10·0) | 0 | 0 | 0 |

30–40). Five (36%) patients had thyroid dysfunction in this group; two had irradiation alone, one had irradiation with vincristine, and two had irradiation with vincristine and lomustine. There was no apparent difference in age at treatment, follow up period, chemotherapy used, irradiation dose, or fractions between those who did or did not develop thyroid dysfunction.

*(B) Hodgkin's disease patients (n=13)*
Five patients had chemotherapy alone or chemotherapy plus radiotherapy away from the thyroid area and all but one had normal thyroid function; the exception was a child who had a diagnostic lymphangiogram. Four patients had chemotherapy plus mediastinal irradiation of 35 Gy and one had thyroid dysfunction. Four patients had radiotherapy in excess of 24 Gy (mean 35 Gy) involving the thyroid area and all had thyroid dysfunction. A total of four patients had lymphangiograms (three also had radiotherapy in excess of 38 Gy to the thyroid area) and all have developed hypothyroidism.

*(C) Leukaemia patients*
*Acute myeloid leukaemia (n=6)*—Three patients had chemotherapy alone and all had normal thyroid function. Two patients had chemotherapy plus total body irradiation (a mean dose of 10·7 Gy in one fraction) and one of them had thyroid dysfunction. The sixth patient had spinal irradiation (12 fraction of 2 Gy in 30 days) and he had thyroid dysfunction.

*Acute lymphoblastic leukaemia (n=8)*—All received radiotherapy involving the thyroid area in 12 fractions during brain or whole central nervous system irradiation for meningeal disease. Only two had thyroid dysfunction having received 23 and 30 Gy to the thyroid respectively. The remaining six patients' radiotherapy dose was 10–18·1 Gy.

*(D) Rhabdomyosarcoma patients (n=9)*
Five patients received radiotherapy involving the thyroid gland (20–56 Gy). Three who received 50–56 Gy became hypothyroid; the other two patients received 20 Gy to the thyroid area and both had normal thyroid function. Four patients received radiotherapy away from the thyroid gland and they had normal thyroid function.

*(E) Bone tumours (n=10)*
All had received intensive chemotherapy alone or in combination with radiotherapy not involving the thyroid gland area. All had normal thyroid function.

*(F) Cerebral tumours (n=3)*
All had received intensive chemotherapy and a very small dose of irradiation to the thyroid area (40–240 cGy). All had normal thyroid function.

## Discussion

The improved survival of children with neoplastic disease has been accompanied by an increase in the side effects of treatment and this includes endocrine disease.[2 3 7 8] In particular children who have had external beam irradiation to the neck may become hypothyroid[3 9] and develop thyroid neoplasms.[6] Although the thyroid gland is relatively radioresistant, its sensitivity is influenced by mitotic activity so that the gland is more vulnerable during its growth in childhood.[10]

We have found a prevalence of thyroid dysfunction after external irradiation to the neck of 40%; other reports vary from 16·5[11] to 97%.[10] These wide differences reflect variables such as dose of irradiation, age of the patient, length of follow up, and possibly the sensitivity of the laboratory tests. Some authors have made a distinction between compensated and true hypothyroidism,[12 13] and they report the prevalence of compensated hypothyroidism to be between 29–44%.[12–14] Our figure of 25% is similar in this respect.

The mechanism by which hypothyroidism develops after irradiation to the neck—whether due to vascular damage, impairment of regeneration, or immunologic reaction—is not clear.[15] Rubin and Casarrett suggested that thyroid irradiation damages both capillaries and endothelium, and that with small doses regeneration takes place.[16] They suggested that with larger doses, however, the residual vascular damage is responsible for a second phase of degeneration of the follicular epithelium and subsequent decrease of thyroid function. In our series the dose of irradiation was important and all those who had had an irradiation dose to the thyroid gland of 40 Gy have developed thyroid dysfunction.

The association between lymphangiography and an increased incidence of hypothyroidism has been documented a number of times.[14 17] The fat soluble organic iodide used in the lymphangiogram remains in the body for several months, and with its slow and continuous release from lymph nodes it leads to chronic iodide load to the thyroid gland (Wolff-Chaikoff block) causing hypothyroidism.[17] Hodgkin's patients are particularly at risk of hypothyroidism if their disease involves the cervical nodes because they are exposed to both irradiation and lymphangiography. Our study confirms earlier reports that there is an increased incidence of thyroid dysfunction in Hodgkin's disease patients, 46% (six out of 13 patients) when compared with

24% (12 out of 50 patients) in non-lymphomatous extrathyroidal neoplasia.

There are relatively few studies on the effects of chemotherapy on thyroid function. Coffey reported two patients who had become hypothyroid after cyclophosphamide treatment.[18] Sutcliffe *et al* examined two groups with advanced Hodgkin's disease treated solely with chemotherapy.[19] The retrospective group (mean follow up of 35 months) had a modest rise in concentration of thyroid stimulating hormone in 44% but in the prospective group all the patients had normal thyroid function. Iodine based investigation and the total amount of treatment were similar in both groups. They commented that this difference may have been due to the longer length of follow up in the retrospective group.

Schimpff *et al* found no increase in thyroid dysfunction when chemotherapy was given as an adjuvant to irradiation, but they do not mention the follow up period.[20] In our study cytotoxic chemotherapy does not appear to have caused any clinical or biochemical evidence of hypothyroidism but the mean follow up is still relatively short. Longer follow up studies should clarify this.

Thyroid dysfunction is a major complication of neck irradiation and requires early detection to minimise potential sequelae. The immediate morbidity is relatively benign with a decrease in height velocity once thyroxine concentrations fall below the normal range. Long term complications may be serious, however, because raised thyroid stimulating hormone concentrations appear to have a permissive role in the development of thyroid neoplasia.[21] There are a number of reports on the development of thyroid carcinoma after irradiation to the neck,[21 22] and it is possible that a damaged gland continuously stimulated by raised concentrations of thyroid stimulating hormone may be at a greater risk of adenomatous and carcinomatous changes.

We believe that all patients who have received irradiation to the neck should have their thyroid function assessed annually for an indeterminate period, and that those with persistently raised thyroid stimulating hormone concentrations (which may rise transiently immediately after irradiation to the neck) should receive thyroid hormone replacement. As the peak incidence of thyroid carcinoma occurs 20 to 30 years after radiation exposure[22] indefinite follow up is essential and palpation of the thyroid gland included at every examination.

Our study and others suggest that the thyroid gland appears to be relatively immune to the common cytotoxic agents used for cancer treatment, but this can only be clarified by long term studies.

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# Follow up study of cardiac involvement in Emery-Dreifuss muscular dystrophy

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SUMMARY A patient with Emery-Dreifuss muscular dystrophy was followed up from 9 to 26 years of age. Serial electrocardiographic studies showed changes ranging from early cardiac conduction abnormality as first degree atrioventricular block to sick sinus syndrome. In addition the development of cardiomyopathy was documented by electrocardiographic, echocardiographic and radionuclide studies of the heart.

Emery-Dreifuss muscular dystrophy is a rare X linked condition clinically distinct from Duchenne and Becker muscular dystrophies.[1] Onset is in childhood and cardiac involvement with conduction disturbances is a frequent and serious complication with a risk of sudden death.[2]

We encountered a 9 year old boy with characteristics of this disorder who later developed cardiomyopathy. Serial electrocardiographic, echocardiographic, and radionuclide studies were useful for estimating the degree of conduction disturbance and cardiomyopathy and predicting the prognosis. Although there are many reports of conduction disturbance in Emery-Dreifuss muscular dystrophy,[2] serial studies of cardiac involvement are rare. We describe a follow up study of our patient from 9 to 26 years of age.

## Case report

A 9 year old boy was admitted to Utano National Hospital for motor disability. There was neither consanguinity nor a history of neuromuscular disorders in his family. He was born at 35 weeks' gestation by vaginal delivery after a normal pregnancy, and his birth weight was 1900 g. His motor milestones were delayed and he was unable to walk unaided until 2½ years of age. His intellectual development was normal. A waddling gait was noticed at the age of 4 years and he underwent Achilles tenotomy for relief of severe talipes equinovarus at 8 years of age. Muscle biopsy specimens obtained at that time from the quadriceps and gastrocnemius muscles showed a pronounced variation in the fibre size associated with many central nuclei, moderate perimysial fibrosis, and fatty infiltration.

Physical examination on admission showed abnormal neck posture and limited neck flexion, difficulty in climbing stairs, elbow contracture, and muscle wasting with a predilection for the shoulder girdle and peroneal muscles. Deep tendon reflexes could not be elicited. The serum creatine kinase activity was slightly raised. His heart rate was 73 beats/minute (bpm) and an electrocardiogram showed a first degree atrioventricular block with a PR interval of 0·20 seconds (figs 1a and 2a).

At age 17, bradycardia was recognised in the early morning. An electrocardiogram showed atrial standstill with junctional rhythm at a rate of 40 bpm and QS pattern in V2 (figs 1b and 2b). Cardiac catheterisation at that time showed normal ventricular performance. Cardiac output was 3·48 l/minute/m². An electrophysiological study showed elongated sinus recovery time up to 3388 msec; this is evidence of sick sinus syndrome.[3] An echocardiogram also showed normal heart chamber size and performance with a left ventricular ejection fraction of 83% by the method of Pombo *et al.*[4] A demand type cardiac pacemaker was implanted at the chest wall. An endomyocardial biopsy specimen from the right ventricle disclosed a variation in fibre size and focal fibrosis, suggesting the presence of cardiomyopathy (fig 3). An electrocardiogram at age 19 showed QS pattern in V1 to V3 and negative T in II, III, aVF and V3-V6 (figs 1c and 2c). His subsequent course was uneventful and he was discharged from the hospital at the age of 22 years and was able to work part time. At age 24 he developed signs of heart

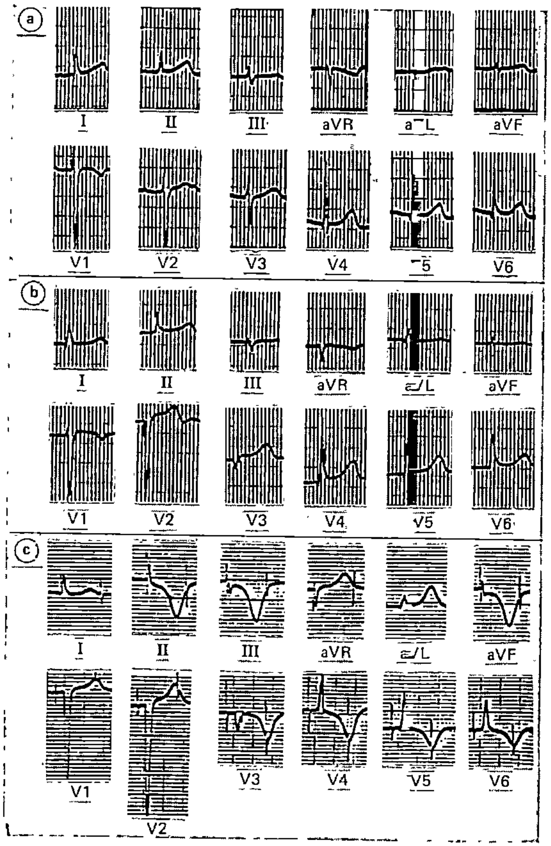

Fig 1 *Serial electrocardiograms: (a) at 10 years 4 months of age, showing the first degree atrioventricular block with PR interval of 0·20 seconds. (b) At 17 years [illegible] months of age, showing atrial arrest with junctional rhythm. QS pattern in V2 and Q wave in V3 were also observed. (c) At 19 years 10 months of age after implantation of a permanent pacemaker. His own beats were shown. No atrial electrical activity was present and QS pattern spread from V1 to V3. Negative T in II, III, aVF and V3-V6 can also be seen.*

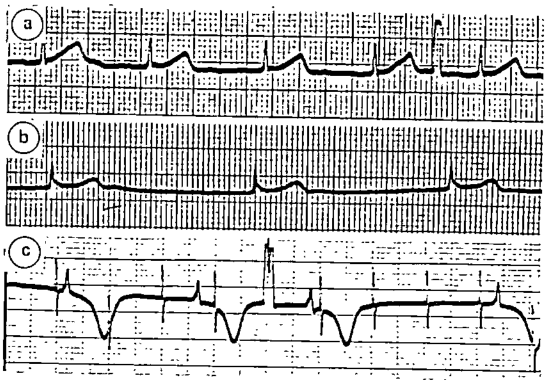

Fig 2 *Longer rhythm strips of (a), (b), and (c) in fig 1; (a) showing sinus rhythm, but (b) and (c) showing nodal rhythm.*

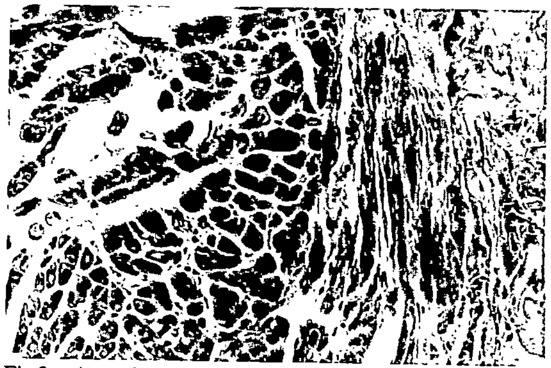

Fig 3 *An endomyocardial biopsy specimen of the right ventricle showing a variation in fibre size. Focal fibrosis can be seen on the right. (Haematoxylin and eosin stain ×900.)*

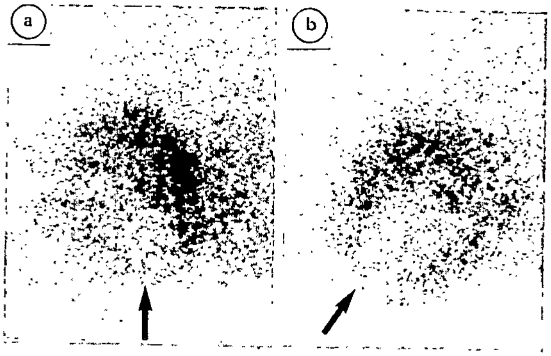

Fig 4 *Thallium imaging at 26 years 6 months of age; (a)=anterioposterior and (b)=left anterior oblique 45°. Perfusion defect was observed from apex to posteroinferior portion (arrows).*

failure and digitalis and diuretics were prescribed. An echocardiogram at age 25 showed a left ventricular ejection fraction of 66% by the method of Pombo *et al*. Gated blood pool scanning showed a dilated left ventricle with a left ventricular ejection fraction of 35% and generalised left ventricular hypokinesis with apical akinesis. Thallium imaging disclosed a pronounced perfusion defect of the cardiac muscle from the apex to the posteroinferior wall. Re-examination at the age of 26 showed a larger perfusion defect (fig 4). On the other hand motor disability of the patient developed slowly, and he was ambulant until 24 years of age. He was readmitted at the age of 25 years 11 months because of an appreciable progression of heart failure and pneumonia. His left ventricular ejection fraction decreased to 17% on echocardiography by the method of Pombo *et al* at age 26, and pronounced tricuspid and mild mitral valve regurgitation were recognised by colour flow mapping. He died at the age of 26 years and 9 months.

## Discussion

The clinical signs observed in our patient meet the criteria of Emery-Dreifuss muscular dystrophy.[5] We observed his progressive deterioration by electrocardiography from an early cardiac conduction abnormality, manifest as first degree atrioventricular block, to sick sinus syndrome. In addition, development of cardiomyopathy was clearly disclosed by electrocardiography. Cardiac catheterisation and an echocardiogram, on the other hand, showed normal cardiac performance at age 17 when a permanent pacemaker was implanted. A specimen of the myocardium obtained at that time disclosed focal fibrosis, suggesting the presence of cardiomyopathy. Cardiomyopathy was also found by serial thallium imaging. Serial echocardiograms and gated blood pool scanning showed a rapid decrease of his left ventricular ejection fraction from the age 25 to 26 years and left ventricular hypokinesis. Although pronounced myocardial fibrosis has been described at necropsy[6 7] or on myocardial biopsy,[8] our patient clearly showed progressive cardiomyopathy in addition to defects in rhythm and conduction. A permanent cardiac pacemaker is effective in preventing sudden death due to profound bradycardia and syncope, but no effective treatment has been found at present for progressive cardiomyopathy. It is the cardiac involvement, not the systemic myopathy, that places the patient at risk. In future heart transplantation might be considered for the treatment of cardiomyopathy found in this syndrome if disorders of voluntary muscle were not considered to be an important irreversible dysfunction of major organs.[9] Donor selection, however, might be a problem.

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# Dietary treatment of hyperlysinaemia

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SUMMARY We describe the lysine restricted, dietary management of three out of four siblings who were identified as having hyperlysinaemia. The diets, started in the neonatal period, were maintained for varying periods with unpredictable success. The propositus, who was not treated, was diagnosed at the age of 5 years, by which time he was already severely handicapped, presumably because of his metabolic disorder. Tentative recommendations are put forward for the management of this seemingly rare disorder. Mild chronic ammonia toxicity may be a factor in the pathogenesis of this condition.

The importance of hyperlysinaemia as a direct or indirect cause of neurological damage and mental retardation is open to dispute. Previous reports provide conflicting data,[1-5] and while not stating unequivocally that hyperlysinaemia is entirely benign more recent evidence, from a large review of 10 cases identified by neonatal screening programmes or family surveys, suggests that the relationship is coincidental.[6] It has also been stated that there is no evidence supporting the use of a low protein diet to reduce plasma lysine concentrations.

We report the dietary management, by lysine restriction, of three affected siblings in a Pakistani family, in which the propositus was found to have hyperlysinaemia during investigations for profound mental and physical handicap. The development of these children has been carefully monitored during periods on and off treatment.

## Subjects and methods

The family tree is shown in fig 1. The parents are first cousins. The propositus, K, was born in Pakistan as were his two elder siblings, both of whom died in early infancy, the first of a chest infection and the second after recurrent convulsions. His birth was said to have been normal but from the age of 2 months he developed convulsions, although he does not seem to suffer from them now. He presented to us at the age of 5 years with severe mental and physical handicap, being unable to walk unsupported or talk and, on clinical examination, had a developmental age of 10 months. He was thin and underweight with no dysmorphic features. He had a moderate increase in adductor muscle tone and hyper-reflexia in both legs. His hearing was thought to be normal but he had poor vision. No possible cause for his retardation other than hyperlysinaemia was found on investigation. He was not treated with a diet and subsequently showed no clinical improvement (table 1). Unfortunately he developed bilateral massive retinal detachment, which was confirmed by pathological examination after enucleation of one eye because of a suspected but disproved tumour. Recently, computed tomography has shown low density changes in the white matter of the cerebrum suggestive of demyelination. There was also evidence of mild shrinkage of the cerebellum and brain stem.

Three of the remaining four younger siblings, all of whom were born in the United Kingdom, were shown by screening soon after birth to have hyperlysinaemia. Thereafter, they were treated with a lysine restricted diet in an effort to prevent neurological sequelae. Their developmental progress was very carefully monitored by one of us (NB), using

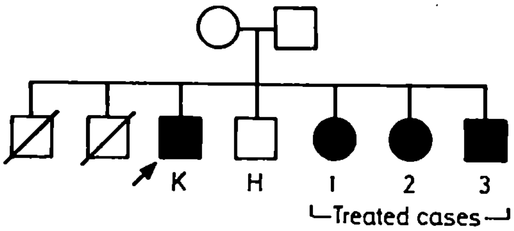

Fig 1 *Family pedigree. K is the propositus; his brother, H, had no evidence of hyperlysinaemia. The two older siblings died in early infancy.*

Table 1 *Griffiths's psychometric assessment of propositus and his affected siblings*

| *Case No* | *Chronological age (months)* | *Griffiths's mental age (months)* | *Griffiths's intelligence quotient* |
|---|---|---|---|
| Propositus | 126·0 | 9·5 | 30·0 |
| Case 1 | 19·0 | 19·8 | 104·0 |
| | 21·0 | 21·5 | 102·0 |
| | 22·0 | 23·0 | 104·5 |
| | 24·0 | 24·1 | 100·4 |
| Case 2 | 2·5 | 3·7 | 148·0 |
| | 7·5 | 9·5 | 125·0 |
| | 14·5 | 16·0 | 114·3 |
| | 17·0 | 17·9 | 105·3 |
| | 20·0 | 17·9 | 89·5 |
| Case 3 | 5·0 | 5·0 | 100·0 |

the Griffiths's scale of mental development. This surveillance was continued after the low lysine diets were discontinued. The fourth child, H, was not shown to have evidence of hyperlysinaemia, after repeated plasma amino acid analyses up to the age of 7 months, and has subsequently made normal developmental progress.

The diagnosis of hyperlysinaemia in the propositus was made after detailed biochemical studies that have been reported by Gray *et al.*[7] Plasma lysine concentration was greatly raised and was shown by in vitro studies in fibroblasts to be caused by a deficiency of lysine oxidation.[7]

In this study fasting plasma lysine concentrations were monitored in the affected siblings by the methods reported above. At the same time plasma ammonia concentrations were also monitored by a standard enzymatic method based on the reductive amination of α-ketoglutarate using glutamate dehydrogenase and reduced nicotinamide adenine dinucleotide.

The low lysine diets were constructed by following the principles used in the management of other amino acid disorders. A lysine free amino acid mix (Scientific Hospital Supplies) was used to provide the equivalent of 3 g of protein/kg of body weight/day, during the first year of life. Lysine was provided in the form of small measured amounts of standard formula baby milk. Initially 88 mg of lysine/kg of body weight/day was permitted, this being the lower limit of theoretical requirement for a normal infant. Energy requirements were ensured by the addition of glucose polymers and fat emulsion. This mixture was supplemented with vitamins (three Ketovite tablets and 5 ml Ketovite liquid per day, Paines and Byrne), minerals, and trace elements (Aminogran Mineral Mix, Allen and Hanbury).

As lysine occurs in all proteins, the provision of a weaning diet presented difficulties. All protein rich baby foods and solids were avoided and the bulk of protein requirements continued to be provided by the lysine free amino acid mix. To this were added controlled amounts of low protein foods such as rice and potatoes, which contain known amounts of lysine.[8] Foods containing very small amounts of protein such as fruit were allowed freely. Energy intake was maintained by the addition of low protein bread and biscuits. In the latter half of the first year of life and thereafter, in an effort to promote tighter control of plasma lysine concentrations, it was found possible to reduce the dietary intake of lysine to as little as 40 mg/kg of body weight/day.

## Results

### CASE 1

This girl was born at term after an uneventful pregnancy and delivery. She was diagnosed at the age of 4 days and a low protein diet from 2 weeks of age, followed by a low lysine diet from 7 weeks of age started. Variations in the low lysine diet and corresponding plasma lysine concentrations are shown in fig 2. Mean ammonia concentrations compared with cases 2 and 3 are shown in table 2. Her diet was formally stopped at the age of 22 months after the birth of her younger sister (case 2). The subsequent rise in plasma lysine concentrations to seven to eight times the normal range confirmed that, to a certain degree, the low lysine diet had been adhered to at home.

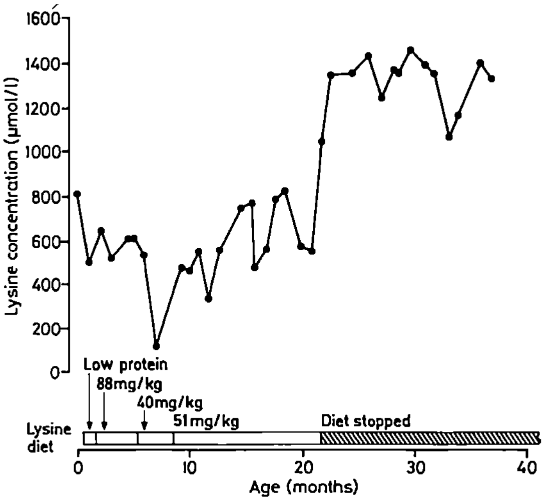

Fig 2 *Case 1: diet and monthly plasma lysine concentrations (normal range at >4 months of age, 45–150 μmol/l).*

Table 2 *Mean plasma ammonia concentrations in the three affected siblings*

| *Case No* | *Mean (SD) ammonia concentration (µmol/l)* | *No of estimations* |
|---|---|---|
| 1 | 52·9 (21·9) | 81 |
| 2 | 70·3 (52·1) | 48 |
| 3 | 63·7 (15·0) | 11 |

Her developmental progress as measured on the Griffiths's scale has been and remains satisfactory (table 1). Her performance on items requiring speech was below average—this was mainly due to her language difficulties experienced as a result of being reared in a mixed language environment. Her growth has been normal, with height and weight on the 50th centile. A computed tomogram at the age of 3 years and 4 months showed no abnormality. She remains well after being on a normal diet for 20 months.

CASE 2

This girl also had an unremarkable perinatal history. She was diagnosed and started on a low lysine diet at 2 weeks of age. Variations in the diet and plasma lysine concentrations are shown in fig 3. Despite plasma lysine concentrations four times the normal range, formal psychometric assessment at 17 months of age confirmed the clinical impression of normality (table 1) and so the diet was stopped on a trial basis. After three months off the diet, however, there was evidence of deterioration of locomotor skills, lack of progress in cognitive skills (table 1), and clinical assessment showed signs of an early spastic diplegia. The diet was recommenced which resulted in a 75% drop in plasma lysine concentrations. A computed tomogram showed evidence of a patchy demyelination of the pons. Resumption of the diet has not yet resulted in her regaining her lost locomotor skills.

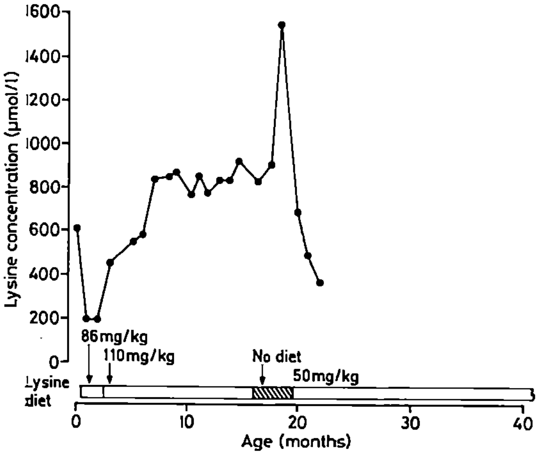

Fig 3 *Case 2: diet and monthly plasma lysine concentrations (normal range at >4 months of age, 45–150 µmol/l).*

So far there appears to have been no deleterious effect on her intellectual development. Although the Griffiths's intelligence quotient scores in table 1 show a steady decline over the five assessments, this decline was wholly accounted for by language difficulties up to the age of 17 months when the diet was discontinued. Her scores on the hearing and speech subtest showed a similar pattern to her sister (case 1). The final Griffiths's score reported was severely affected by loss of locomotor skills. She made fewer gains than on previous occasions on the cognitive subtests but her performance remained within the normal range. Her growth has been unaffected with height and weight increasing steadily along the 25th centile.

CASE 3

This boy was also diagnosed as having hyperlysinaemia at 5 days of age after a normal, term delivery. Since being on a low lysine diet from 1 week of age, developmental assessment at 5 months of age shows him to be within the normal range. His plasma lysine concentrations have also climbed to nearly four times normal. Recently his lysine intake was reduced from 88 to 45 mg/kg of body weight/day after the discovery of low density areas on computed tomography; this suggests the possibility of some pontine atrophy. Thus far he has no neurological signs and in particular his muscle tone and tendon reflexes are normal.

## Discussion

Doubt exists as to whether persistent hyperlysinaemia can itself produce adverse neurological or physical effects.[1–5] Nevertheless, because of the possible causal relation between the hyperlysinaemia and neurological abnormalities in the index case K, we have closely and continuously monitored the progress of the other three affected children.

Interpretation of our recorded plasma lysine concentrations is very difficult because of considerable variation in values, almost all of which are very much above the range for normal children. Case 1 appears to show beyond doubt that exceedingly high concentrations up 1500 µmol/l can be tolerated with no apparent ill effect for a year or more. It might, however, be relevant that this child was only exposed to these persistently high concentrations after the process of brain myelination was completed at about the age of 2 years. It must also be remembered that the deterioration of motor skills and the appearance of abnormal physical signs in case 2 occurred only after she had been exposed to such high concentrations at the earlier age of 15 months—that is, theoretically before brain myelination had been completed (fig 3). These observations must also be compared with our experience of case 3. He already showed some suggestion of demyelination at the age of 7 months, even though his plasma lysine concentrations did not exceed 1000 μmol/l.

It has been suggested that neurological impairment might be produced by exposure to long term, low level ammonia intoxication.[7] In the propositus, although there was no postprandial increase in ammonia concentrations, raised concentrations of about 80 μmol/l were recorded before and after eating (normal less than 47 μmol/l). Standardised fasting ammonia concentrations have therefore been recorded in the other three affected children. Our data (table 2) suggest that ammonia concentrations may be of significance as both cases 2 and 3 have higher mean plasma ammonia concentrations than the unaffected case 1. The difference between cases 1 and 2 is significant ($t=2{\cdot}19$, $p<0{\cdot}025$). The distribution of mean plasma ammonia concentrations certainly appears to follow the pattern of clinical and developmental observations in a more understandable manner.

It is impossible with our limited and variable data to identify a critical ammonia concentration but it may be pertinent to note that case 1 has only had values of plasma ammonia of 100 μmol/l or more recorded on four occasions, all of which occurred after the age of 21 months, whereas case 2 has encountered such concentrations on seven occasions all of which were in her first 14 months of life. Thus far case 3 has only had one concentration of 100 μmol/l, which occurred at age 6 months. Regression analyses have shown no direct relationship between coincidental plasma lysine and ammonia concentration in these children ($r=0{\cdot}28$, $n=75$ for case 1 and $r=-0{\cdot}15$, $n=41$ for case 2). Also, neither blood concentration has appeared to be particularly raised during intercurrent illnesses, including upper respiratory tract infections and diarrhoeal illness. On four occasions, case 2 has had plasma ammonia concentrations greater than 150 μmol/l and on one occasion, a value of 320 μmmol/l was recorded. On none of these occasions did she appear to be particularly unwell.

The cause of the hyperammonaemia may be secondary to the competitive inhibition of arginase by high concentrations of lysine, thus interfering with ammonia elimination through the Krebs urea cycle.[9] This was the suggested explanation for the one documented case of periodic hyperlysinaemia associated with hyperammonaemia reported by Colombo *et al*,[10] but this explanation has been challenged by results from in vitro studies.[11] The lack of clinical or biochemical evidence of hyperammonaemia in other reported patients with persistent hyperlysinaemia is difficult to interpret. Most of these patients were not handicapped or if they were, had no ammonia studies done.[1-6] Certainly our cases would appear to be different from that of Colombo *et al* in that the hyperlysinaemia is persistent despite dietary measures and not associated with profound episodes of vomiting and coma when ammonia concentrations are raised. Instead, our cases appear to represent an intermediate situation between the two previously described types of hyperlysinaemia.

We have concern about compliance at home with the relatively complex low lysine diet. Planned and unplanned admissions to hospital and the employment of a 'linkworker' for the family who regularly visits the home, however, have not led to very significant changes in plasma lysine concentrations. It is also of note that when these children have been deliberately taken off their diets their plasma lysine concentrations have risen considerably.

It is extremely difficult to come to any firm conclusions about the management of young children with this disorder but in view of the severe developmental and physical problems of the index case and the possible developing problems in two of the other three affected children, some form of effective treatment must be sought. Our experience so far would tend to indicate that treatment with a low lysine diet may well be worthwhile and that plasma lysine concentrations are probably best kept well below 1000 μmol/l in the first 2 years of life. Also during the same period plasma ammonia concentrations should be monitored and if possible kept below 100 μmol/l and probably much lower. Unfortunately, in our experience, the plasma ammonia concentration does not seem to respond to dietary manipulation as well as plasma lysine concentrations.

We thank the staff of the department of chemical pathology, Sheffield Children's Hospital for measurement of plasma lysine concentrations and Dr G Bonsor and the staff of the neuroradiology department at Pinderfields Hospital, Wakefield for the computed tomograms.

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# Echocardiographic assessment of infants born to diabetic mothers

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SUMMARY Echocardiography was carried out in 31 neonates (group 1) born to diabetic mothers and 37 control infants (group 2) matched for weight and gestational age. The interventricular septum was significantly thicker in group 1 babies (mean (SD) 4·77 (1·4) mm) compared with those in group 2 (2·5 (0·7) mm); in eight it was more than 5 mm, but had regressed in six over a period of three months. There was no significant difference between the two groups in the left ventricular internal dimension, right ventricular outflow tract, or size of the left atrium or the aorta. The left ventricular mass was significantly greater in infants born to diabetic mothers. The left ventricular contractility (judged by the percentage of shortening of the internal dimension and the ejection fraction) was significantly greater in group 1. No evidence of left ventricular outflow obstruction was found on pulse Doppler echocardiography in group 1.

Infants born to diabetic mothers have an increased risk of developing congestive cardiac failure.[1] Myocardial dysfunction (tachypnoea and tachycardia) may be caused by primary cardiac disease or secondary to hypoxia, polycythaemia, or metabolic disturbances. Echocardiographic studies in these infants show thickened (>5 mm) interventricular septums and thickening of the right and left ventricular free walls with disproportionate septal hypertrophy in 25–30% of cases.[2-4]

We carried out a prospective echocardiographic study of infants born to diabetic mothers and compared the results with those from normal newborn infants born at full term.

## Patients and methods

Infants from 31 consecutive births to mothers with overt diabetes mellitus or gestational diabetes that took place at the All India Institute of Medical Sciences Hospital were studied prospectively. These patients were selected from the group of high risk pregnant women at our antenatal clinics. All the women were routinely screened for diabetes mellitus using fasting and postprandial blood glucose concentrations. The borderline cases were subjected to oral glucose tolerance tests.[5] Insulin was given to all overtly diabetic mothers, but gestational diabetes was managed by dietary control alone.

A group of 37 infants matched for gestational age and born after uncomplicated delivery immediately preceding or following the index case, served as controls. None of the mothers of these infants had diabetes mellitus. Clinical examination did not show any congenital malformations.

All deliveries were attended by a paediatrician well versed in techniques of resuscitation. Apgar scoring at birth was recorded in all, and none of the babies had birth asphyxia. All babies who had uncomplicated deliveries were nursed with their mothers in the maternity ward. All infants born to overt or gestational diabetic mothers, and infants in the control group who were small for gestational age or large for gestational age were screened for hypoglycaemia at 1–2 hours, 6–8 hours, 24 hours, and 48 hours. Hypoglycaemia was treated according to the prevailing practice of our unit.[6]

Echocardiographic studies were performed using an ATL ultramark '8' system equipped with a combined cross sectional imaging and pulsed Doppler transducer using a 5 MHz transducer, at a mean (SD) age of 3 (1·5) days, and recordings made on video tape at a speed of 100 mm/s. Echocardiographic meaurements were made from these using standard techniques (figs 1 and 2).[7] Doppler velocities were measured across mitral, tricuspid, pulmonary, and aortic valves and all infants were carefully screened for any gradient across the left ventricular outflow tract.

Left ventricular function was assessed by calcula-

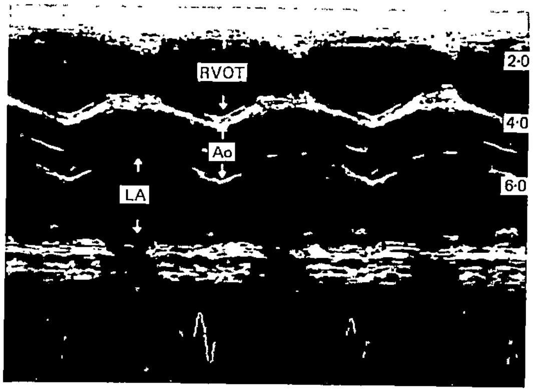

Fig 1 *M mode echocardiogram showing aortic and right ventricular outflow tract dimensions at the end of diastole and left atrial dimension at the end of systole. RVOT=right ventricular outflow tract, AO=aorta, LA=left atrium.*

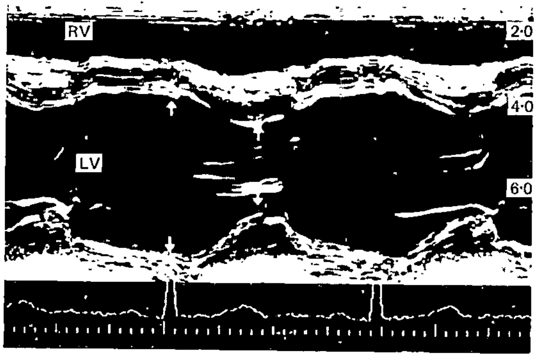

Fig 2 *M mode echocardiogram showing left ventricular internal dimensions at the end of diastole and the end of systole. RV=right ventricle, LV=left ventricle.*

ting the percentage shortening of the internal dimension[8] and the ejection fraction.[7] The percentage shortening of the internal dimension equals the left ventricular internal dimension at the end of diastole minus that at the end of systole divided by the dimension at the end of diastole and multiplied by 100. The ejection fraction is calculated by the same formula except that all values (except 100) are cubed.

The left ventricular mass was calculated by cubing the sum of the left ventricular internal dimension, the thickness of the interventricular septum and the thickness of the left posterior wall (all at the end of diastole), subtracting the cubed value for left ventricular internal dimension at the end of diastole, and multiplying by 1·05.[9]

Septal hypertrophy was defined as a septal thickness of 5 mm or more.[10] Newborn babies in whom the interventricular septum at the end of diastole measured 5 mm were followed up at four to six weeks, and at 3 months of age. Statistical analysis was by Student's *t* test.

## Results

Five babies were born to mothers with diabetes mellitus and 26 to mothers with gestational diabetes; there were 17 girls and 14 boys. Four were born at <37 weeks' gestation and 27 were born at full term. The mean (SD) gestational age was 38·2 (1·5) weeks, range 35 to 40. The mean weight was 3340 (79) g, and 10 infants were large for gestational age, two small, and 19 normal.

Thirty seven control infants (20 girls and 17 boys) were evaluated echocardiographically. Four were born at <37 weeks' gestation and 33 were born at full term. Their mean gestational age was 38·1 (0·4) weeks, range 35 to 40. Their mean weight was 3070 (43) g, with four infants large for gestational age and the rest normal.

The mean weight and gestational age were not significantly different in the two groups ($p>0{\cdot}05$).

In normal control infants the mean thickness of the interventricular septum was 2·5 (0·7) mm; even among those infants large for gestational age the thickest was 4·3 mm. This infant weighed 4200 g. By contrast in the infants born to diabetic mothers the mean thickness was 4·7 (1·4) mm ($p<0{\cdot}001$), and even in one infant who was small for gestational age, weighing only 2400 g, the thickness was 7·1 mm. Eight infants (25%) born to diabetic mothers had thicknesses of more than 5 mm. The left ventricular posterior wall in systole was thicker in infants of diabetic mothers. Other echocardiographic dimensions were not significantly different between the two groups (table 1).

Left ventricular contractility as assessed by the ejection fraction and percentage shortening of the internal dimension was significantly higher in infants of diabetic mothers compared with the controls, and the left ventricular mass was significantly greater ($p<0{\cdot}001$).

Doppler velocities were normal across all valves in both groups and there was no evidence of left ventricular outflow tract obstruction by Doppler even in patients with thickened septums.

Of the eight patients with thickened septums on initial examination, six were followed up by serial echocardiograms at four to six weeks and at 3 months. The septal thickness had decreased in all six to below 5 mm. This was noticed within six weeks in four and within three months in the other two infants.

Table 1 *Mean (SD) echocardiographic measurements in infants of diabetic mothers and controls*

| | *Infants of diabetic mothers (n=31)* | *Control infants (n=37)* | *p Value* |
|---|---|---|---|
| Left ventricular internal dimension (mm): | | | |
| At the end of diastole | 15·1 (2·6) | 13·8 (2·2) | NS |
| At the end of systole | 8·8 (1·8) | 8·5 (1·5) | NS |
| Thickness of interventricular septum (mm): | | | |
| At the end of diastole | 4·7 (1·4) | 2·5 (0·7) | <0·001 |
| At the end of systole | 6·1 (1·8) | 3·8 (0·8) | <0·001 |
| Thickness of left ventricular posterior wall (mm): | | | |
| At the end of diastole | 2·7 (0·7) | 2·5 (0·7) | NS |
| At the end of systole | 3·9 (1·0) | 3·3 (0·7) | <0·001 |
| Diameter of aorta (mm) | 9·2 (1·4) | 8·4 (1·6) | NS |
| Width of left atrium (mm) | 8·2 (1·8) | 8·2 (1·9) | NS |
| Width of right ventricular outflow tract (mm) | 11·0 (2·4) | 9·9 (1·9) | NS |
| Interventricular septum:left ventricular posterior wall ratio | 1·79 (0·45) | 1·18 (0·36) | <0·001 |
| Percentage shortening of internal dimension | 43·88 (8·04) | 38·22 (6·59) | <0·01 |
| Percentage ejection fraction | 81·54 (8·31) | 74·53 (8·71) | <0·01 |
| Left ventricular mass (g) | 8·41 (3·97) | 4·15 (1·81) | <0·001 |

Table 2 *Mean (SD) echocardiographic measurements in infants of diabetic mothers with and without hypoglycaemia*

| | *Infants with hypoglycaemia (n=7)* | *Infants without hypoglycaemia (n=24)* | *p Value* |
|---|---|---|---|
| Birth weight (g) | 3670 (730) | 3210 (790) | NS |
| Left ventricular internal dimension (mm): | | | |
| At the end of diastole | 15·2 (2·6) | 16·9 (3·0) | NS |
| At the end of systole | 8·5 (1·8) | 8·9 (1·9) | |
| Thickness of interventricular septum (mm): | | | |
| At the end of diastole | 4·6 (1·5) | 4·8 (1·2) | NS |
| At the end of systole | 5·8 (1·8) | 6·2 (1·9) | NS |
| Thickness of left ventricular posterior wall (mm): | | | |
| At the end of diastole | 2·5 (0·6) | 3·2 (1·0) | <0·05 |
| At the end of systole | 3·8 (0·9) | 4·0 (1·1) | NS |
| Diameter of aorta (mm) | 8·8 (1·5) | 9·5 (1·4) | NS |
| Width of left atrium (mm) | 8·2 (1·9) | 8·2 (1·3) | NS |
| Width of right ventricular outflow tract (mm) | 10·5 (2·3) | 11·3 (2·4) | NS |
| Interventricular septum:left ventricular posterior wall ratio | 1·57 (0·48) | 1·86 (0·43) | NS |
| Percentage shortening of internal dimension | 44·13 (8·01) | 43·66 (7·64) | NS |
| Percentage ejection fraction | 80·94 (12·58) | 81·50 (6·56) | NS |
| Left ventricular mass (g) | 9·46 (3·07) | 8·06 (4·23) | NS |

Hypoglycaemia occurred in seven of 31 patients born to diabetic mothers (23%) and in none in the control group. The various echocardiographic dimensions did not differ significantly in patients with or without hypoglycaemia except for the thickness of the left ventricular posterior wall at the end of diastole (table 2).

## Discussion

Echocardiographic data in the present study substantiates the earlier radiographic and histopathological observations describing cardiomegaly in infants born to diabetic mothers.[10] The thickness of the interventricular septum and left ventricular posterior wall thickness were greater than normal, and the ratio of one to the other was significantly more (p<0·001) in infants born to diabetic mothers. This increased myocardial thickness cannot be explained merely by their being large for gestational age because in our series of normal controls, the myocardial thickness in the large babies never exceeded the upper limit of normal value. In addition a small infant born to a diabetic mother had a thickened septum. The left atrial and internal ventricular dimensions were comparable with the dimensions of the normal controls. The left ventricular mass was significantly greater in infants born to diabetic mothers compared with controls ($p<0.001$), and in addition the ejection fraction and percentage shortening of the internal dimension were significantly increased ($p<0.001$), indicating that despite having cardiac enlargement the contractility of the myocardium was enhanced.

Asymmetric septal hypertrophy was first observed in a stillborn infant of a diabetic mother by Maron *et al.*[11] Poor diabetic control has been correlated both with the degree of septal hypertrophy and with the presence of symptoms of respiratory distress.[3] None of our newborns had respiratory distress or congestive heart failure despite having thickened septums.

Hypertrophy of the septum occurred in three of seven babies with hypoglycaemia, but in only five of 24 without hypoglycaemia, and in none of the control babies, suggesting an association between neonatal hypoglycaemia and septal thickness. Breitweser *et al* also showed this association.[12] In the present series the septal thickness in babies who developed hypoglycaemia did not differ significantly from those without it.

Most earlier studies were on M mode echocardiographic equipment. It is likely that with only an M mode echo the internal dimensions and thicknesses may not be correctly identified because the echo beam was not absolutely perpendicular. An M mode echo derived from a cross sectional image overcomes this drawback.

The presence of asymmetric septal hypertrophy in the newborn is not specific for any disorder. Normal infants have been reported to have it if the ratio of septum:ventricular posterior wall $>1.3$. They can be separated from others because they do not have an absolute increase in septal thickness. It may occur in familial cases, glycogen storage disease (type II), and any cause of right ventricular hypertension.[13 14] In diabetes the hypertrophy may be asymptomatic and regress over months. In Pompe's disease it presents at about 3–4 months of age.

Six of the eight infants with septal hypertrophy had evidence of decreasing septal thickness on serial echocardiograms, confirming the earlier reports of the transient nature of the problem.[2 8]

Any infant born to a diabetic mother who also has respiratory distress must have an echocardiogram because congestive cardiac failure can be the result of obstructive or non-obstructive cardiomyopathy. Whether better control of diabetes in the mother leads to a decreased incidence of cardiac hypertrophy needs to be substantiated.

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# Breath hydrogen excretion in infants with colic

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SUMMARY Breath hydrogen excretion as an index of incomplete lactose absorption was measured in 118 healthy infants who were either breast fed or given a formula feed containing lactose, some of whom had colic. Infants with colic (n=65) were selected on the basis of the mother's report of a history of inconsolable crying lasting several hours each day. Infants in the control group (n=53) were not reported to cry excessively by their mothers. Breath samples were collected using a face mask sampling device preprandially, and 90 and 150 minutes after the start of a feed. Normalised breath hydrogen concentrations were higher in the group with colic than in the control group at each time point. The median maximum breath hydrogen concentration in the colic group was 29 ppm, and in the control group 11 ppm. The percentage of infants with incomplete lactose absorption (breath hydrogen concentration more than 20 ppm) in the colic group was 62% compared with 32% in the control group. The clinical importance of the observed association between increased breath hydrogen excretion and infantile colic remains to be determined. Increased breath hydrogen excretion indicative of incomplete lactose absorption may be either a cause or an effect of colic in infants.

Infantile colic is a common but poorly defined condition of unknown cause that occurs in otherwise healthy infants during the first few months of life.[1] It is characterised by paroxysms of excessive and inconsolable crying.

Colic is important as a cause of distress to the infant and parents, it may result in premature weaning or change of formula feed, it may necessitate treatment of the infant, and be a possible stimulus for child abuse or domestic violence.[1–3] Children who have had colic seem to be predisposed to disturbances of sleep and have a 'difficult temperament'.[2 4] Despite these concerns there is no effective behavioural, nutritional, or pharmacological treatment for colic.

Mothers' reports of 'rumbling tummies', excessive flatus, and frothy stools in colicky infants suggest that a possible cause may be carbohydrate malabsorption. Furthermore, the concentration of hydrogen in the breath of healthy infants increases from birth to peak in the second month of life, declining to low concentrations by 3 to 4 months of age.[5] This pattern of breath hydrogen excretion parallels the pattern of crying in infants with colic. Raised concentrations are more frequently detected in the late afternoon or early evening, a time when colic is commonly reported to occur.[5] Hydrogen in the breath of infants is derived exclusively from bacterial fermentation of unabsorbed carbohydrate in the intestine. Its measurement provides a sensitive, reliable, and semiquantitative index of incomplete carbohydrate absorption.[6] Despite the similarities between carbohydrate malabsorption and colic there has been no published study to our knowledge that has compared breath hydrogen excretion in infants with colic and a control group.

We report here a study of breath hydrogen excretion in infants, with or without colic, who were either breast fed or given a formula feed containing lactose. The hypothesis was that infants with colic absorbed lactose less efficiently than control infants.

## Subjects and methods

Healthy, full term infants between 3 and 20 weeks of age, whose growth and development had been normal since birth, and who were breast fed or given a formula feed containing lactose, were eligible for the study. Infants with colic were recruited from a Tresillian Family Care Centre (where infants and their mothers were admitted for mothercraft help), or from baby health centres. These infants were selected if the mother reported a history of inconsolable crying lasting several hours each day for which no clinical cause could be found. Infants in the control (without colic) group were recruited from baby health centres and nursing mothers groups, and were not reported to cry excessively by their mothers. Infants were recruited to the study from July 1985 to June 1987. The following criteria would have excluded an infant from the study: treatment in the past two weeks with an oral antibiotic (n=0), a recent attack of gastroenteritis (n=1), use of an antacid or feed thickener (n=2), weaning in the two weeks before the study (n=2), negative in vitro faecal hydrogen test (n=4), onset of colicky like behaviour after 6 weeks of age (n=5), or incomplete collection of the series of breath samples because of inconvenience or distress caused by the procedure (n=7).

Breath samples were collected in duplicate or triplicate preprandially, and 90 and 150 minutes after the start of the feed. No alteration was made to the feeding regimen. A sampling device comprising an infant face mask (Laerdal No 0, 1, or 2) and a two way valve and port system was used for the collection of breath samples.[7] During sampling the face mask was held firmly over the infant's nose and mouth. Small aliquots (<2 ml) of each tidal volume from late in the expiratory phase were aspirated into a 20 ml syringe fitted with a stopcock until 20 ml had been collected. The breath sample was then transferred to a 20 ml evacuated blood collection tube (Venoject) and stored in a refrigerator until analysis. Breath samples can be stored in these tubes for at least seven weeks.[8] Tubes were marked with a code so that the analysis was done without knowing which group the baby was in. The time of sample collection was also recorded.

Breath samples were analysed for hydrogen and oxygen by gas chromatography within four weeks of collection.[8] The gas chromatograph (Hewlett Packard Model No 5710) was fitted with a thermal conductivity detector. The copper column (3·0 m×6 mm) was packed with molecular sieve 5A 60/80 mesh. The operating temperature was 50°C and the carrier gas was argon (20 ml/minute). A sample of the breath gas was removed from the Venoject tube through a 20 ml gas tight syringe fitted with a locking device. After the syringe had been filled and locked off, the needle was detached and the plunger depressed to the 6 ml mark to raise the gas pressure within the syringe to above atmospheric pressure. The sample was then injected into the 5 ml sampling loop of the gas chromatograph. The instrument was calibrated using a commercial standard of hydrogen (mean (SD) 105 (2) ppm, Commonwealth Industrial Gases) and ambient air (20·9% oxygen). The coefficients of variation for the analysis of the hydrogen standard and air were 4% and <1%, respectively. The detection limit was 2 ppm hydrogen.

Hydrogen concentration was normalised to 18·9% oxygen (the mean in the first 50 subjects) to reduce variability related to sample collection.[7] Normalised hydrogen values of more than 20 ppm were taken to indicate incomplete lactose absorption on the day of sampling.[9] Samples with an oxygen concentration of more than 20% were discarded as technically inadequate.

Fresh stool samples were collected for testing the capacity of the faecal flora to produce hydrogen from lactose in vitro. About 200 mg of faeces were added to a 20 ml Venoject tube containing 1 ml 0.1 M phosphate buffered lactose (pH 7·2) 1·25% w/v, and 2 g sterile glass beads. The tube was closed with its stopper, shaken vigorously for 30 seconds, and incubated at 37°C for one hour. Headspace gas was collected by displacement with water into a 20 ml syringe, transferred to an evacuated Venoject tube, and analysed for hydrogen by gas chromatography. Hydrogen in excess of 100 ppm was chosen arbitrarily as an indicator of in vivo hydrogen producing capability (positive test).

Mothers were asked to complete a questionnaire regarding infant, maternal, and family history. The study protocol was approved by the Royal Society for the Welfare of Mothers and Babies (Tresillian) and the New South Wales Department of Health. Signed consent was obtained from the mother of each infant.

The breath hydrogen data were analysed as a nested factorial design by analysis of variance. Subsequent statistical analysis used the highest mean breath hydrogen value at any time point for each infant (maximum hydrogen) as there was no consistent temporal relationship between breath hydrogen excretion and the start of the feed. The maximum hydrogen values of the infants in the two groups were compared using a two sample Mann-Whitney U test. The effects of age and time on breath hydrogen excretion were examined by linear regression using the maximum hydrogen values. Other data were compared using two sample *t* tests, the equivalent two sided non-parametric test, or an appropriate contingency table.

## Results

The study comprised 118 infants, 65 with colic and 53 who acted as controls.

Breath hydrogen excretion was higher in the colic group than in the control group at each time point ($p<0·025$); the maximum hydrogen values are

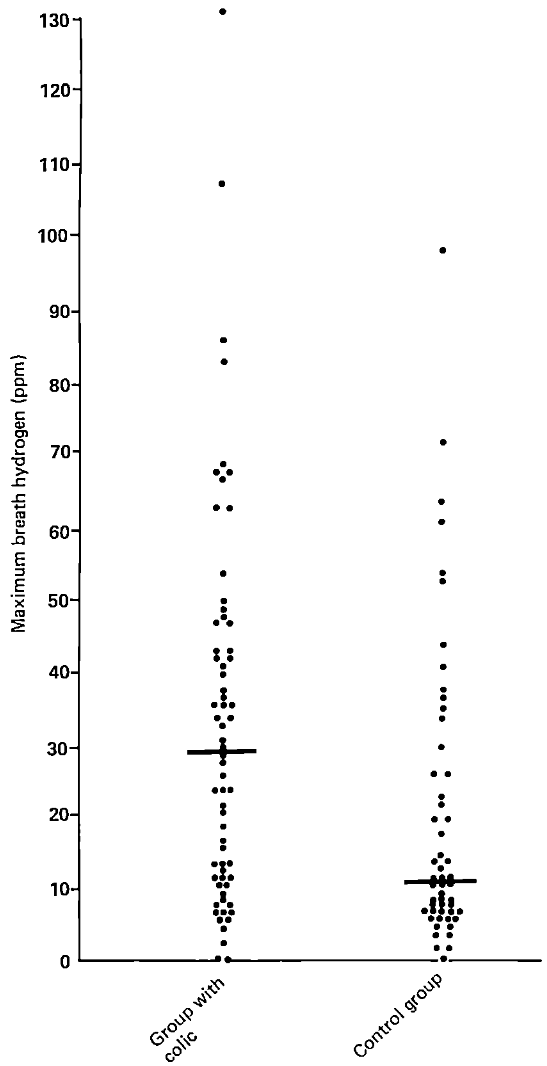

Figure *Maximum breath hydrogen concentrations (ppm) in infants with and without infantile colic. Bars represents the medians (29 in the group with colic and 11 in the control group).*

shown in the figure. The median maximum hydrogen value in the colic group was 29 ppm and in the control group 11 ppm ($p<0{\cdot}001$). The mean (SD) oxygen concentrations in the samples from the two groups were 19·1 (0·7)% and 19·2 (0·6)%, respectively.

The percentage of infants with incomplete lactose absorption (breath hydrogen concentration of more than 20 ppm) in the colic group (62%) was significantly higher ($\chi^2=10{\cdot}15$, $p<0{\cdot}01$) than in the control group (32%).

The characteristics of the infants in the study and aspects of maternal and family history are shown in tables 1 and 2. The infants with colic were younger than the control infants, but there was no correlation between breath hydrogen excretion and age in either group ($r=-0{\cdot}02$). Significantly fewer infants with colic were exclusively breast fed. Eight subjects in the colic group, however, had been weaned on to formula feed in an attempt to alleviate their colicky behaviour. The proportion of first born infants, and of infants whose sibling(s) or parent(s) were reported to have had colic, was significantly higher in the colic group. There were no significant differences between the two groups in family history of allergy, maternal age, obstetric history, or family income, education, or structure.

There were no significant differences between the colicky infants recruited from Tresillian Family Care (n=39) or baby health centres (n=26), or between non-colicky infants from baby health centres (n=43) or nursing mothers groups (n=10).

Preprandial samples were collected at a mean time of 1415 (range 0730–1930) in the colic group, and at 1100 (range 0830–1745) in the non-colic group ($p<0{\cdot}001$). There was no correlation, however, between breath hydrogen excretion and time of sample collection ($r=0{\cdot}06$).

## Discussion

In this study breath hydrogen excretion was significantly greater in infants with colic than those

Table 1 *Characteristics of 65 infants with colic and 53 control infants*

| | *Group with colic (n=65)* | *Control group (n=53)* | *p Value* |
|---|---|---|---|
| No (%) of boys | 36 (55) | 32 (60) | NS |
| No (%) of girls | 29 (45) | 21 (40) | NS |
| Median (95% CI) age (weeks) | 8 (6 to 9) | 9 (7 to 12) | <0·025 |
| Mean (95% CI) birth weight (g): | | | |
| Boys | 3390 (3290 to 3490) | 3670 (3530 to 3820) | <0·025 |
| Girls | 3300 (3170 to 3430) | 3480 (3370 to 3590) | NS |
| No (%) breast fed | 50 (77) | 48 (91) | <0·05 |
| No (%) first born | 41 (63) | 17 (32) | <0·001 |

Table 2 *Maternal and family history in 65 infants with colic and 53 control infants*

| | *Group with colic (n=65)* | *Control group (n=53)* |
|---|---|---|
| Mean (95% CI) maternal age (years) | 30 (29 to 31) | 30 (29 to 31) |
| Mean (95% CI) weight gain during pregnancy (kg) | 12·6 (11·4 to 13·8) | 12·3 (10·6 to 14·0) |
| Mean (95% CI) duration of labour (hours) | 8 (7 to 10) | 8 (6 to 11) |
| No (%) of vaginal deliveries | 54 (83) | 42 (79) |
| No (%) having epidural anaesthesia | 28 (43) | 23 (43) |
| No (%) having forceps deliveries | 19 (29) | 9 (17) |
| No (%) with history of colic in sibling(s) or parent(s), or both | 22 (34) | 7 (13)* |
| No (%) with family history of allergy | 30 (46) | 21 (40) |
| No (%) of families with good income $25–35 000 | 19 (29) | 18 (34) |
| No (%) of families in which either parent had tertiary education | 48 (74) | 35 (66) |
| No (%) of single parent families | 1 (2) | 2 (4) |

*p<0·001.

without. Incomplete lactose absorption was twice as common in the colicky infants as in the control group. In contrast, Liebman found no association between infantile colic and lactose intolerance assessed by faecal pH and reducing substances.[10]

Incomplete lactose absorption in infants with colic may reflect the delayed development of adequate lactase capacity or mucosal damage—for example, being secondary to milk protein allergy. Other factors affecting the delivery of lactose to the colon could also be concerned. These factors include the duration and frequency of feeding, the rate of gastric emptying, and the transit time through the small intestine. Differences in breath hydrogen excretion between colicky and control infants may also be associated with factors other than the amount or rate of delivery of lactose to the colon. The nature of the bowel flora, colonic bacterial metabolic pathways, the partial pressure of hydrogen in the colon, the buffering capacity of the colon, gut perfusion, and incomplete monosaccharide absorption may all play a part.

Colic may result directly from the hyperperistaltic stimulus of the fluid load imposed by the osmotic action of unabsorbed lactose in the small intestine. Alternatively, colonic bacterial metabolism of unabsorbed lactose forming distending gas or pharmacologically active metabolites may be responsible for the signs of colic. Absorption and metabolism of the short chain fatty acid products of bacterial fermentation of unabsorbed lactose in the colon may compensate for the apparent energy loss associated with lactose malabsorption.[11] Absorption of short chain fatty acids stimulates the uptake of water from the colon and is coupled with secretion of bicarbonate into the colon.[12] These factors may explain why an infant who absorbs the lactose in a feed incompletely can continue to thrive and not show any signs of intolerance.

Colic was significantly associated with being first born and with a family history of colic. It was not associated with maternal age, a family history of allergy, or socioeconomic status, this is consistent with other reports.[13] Prolonged labour, forceps delivery, and epidural anaesthesia have also been linked to the subsequent development of colic.[14] These factors and other aspects of obstetric history were not significantly different in the two groups of this study.

There is substantial overlap of breath hydrogen excretion values between the two groups of infants. More than a third (38%) of the infants in the colic group had low values of breath hydrogen while 32% of the infants in the control group had increased breath hydrogen excretion. This may reflect the aetiological heterogeneity of infantile colic. Alternatively, assignment of infants to the colic or control group simply by the mothers' perception of the amount of crying may not clearly distinguish colicky and non-colicky infants.

The clinical relevance of the association between the increased breath hydrogen excretion and infantile colic shown in this study remains to be determined. It may be that elevated breath hydrogen excretion is secondary to colic and is not a reflection of the cause of the behaviour. Studies designed to test whether reduced lactose intake prevents the development of colic or ameliorates established colic are therefore needed.

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# Sonographic finding of ventricular asymmetry in neonatal brain

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SUMMARY One thousand normal Chinese full term neonates underwent prospective ultrasonography examination. Asymmetry of size between the right and left lateral ventricle was observed in a similar proportion of boys: 257/551 (47%) and girls: 183/449 (41%). The mode of delivery did not significantly influence the occurrence of ventricular asymmetry. We propose four different patterns of asymmetry.

It is widely accepted that the cerebral ventricles can be clearly shown by sector ultrasonography and ventricular dilatation can be easily recognised. Several authors have reported that a significant proportion of normal children or neonates had asymmetric lateral ventricles on pneumoencephalography or ultrasonography.[1-3]

## Subjects and methods

During a period of 10 months from March to December 1984, 1000 of 3472 (29%) consecutively delivered neonates in this hospital were scanned by sector sonogram after obtaining informed consent from parents. There were 551 boys and 449 girls who ranged from 35 to 43 weeks' gestation. Their birth weight ranged from 2200 to 4650 g with a head circumference ranging from 30·5 to 38·5 cm. A total of 598 infants were born by normal spontaneous delivery; 160 by vacuum extraction; 30 by forceps; and 212 by caesarean section.

The neonates were examined at the bedside from 2 to 5 days of age with a portable, real time sector sonograph (Aloka SSD-720) with a frequency of 5 MHz and visual field of 80°. Coronal and sagittal views of the brain were obtained by placing the transducer over the anterior fontanelle. The coronal plane at the level of foramen of Monro was selected and ventricular width was recorded at the widest distance perpendicular to the long axis of the lateral ventricle. Angled sagittal planes in both hemispheres parallel to the midsagittal section at the level of the widest occipital horn were chosen and the distance from tip of the occipital horn to the most lateral part of thalamus was recorded as occipital horn size. The size of ventricular body was measured as the distance on the line perpendicular to the longitudinal axis of the lateral ventricle at its midpoint (figure). Data from the sagittal planes, where the ventricular body and occipital horn can be well defined, were collected for the present analysis. Asymmetry of ventricles was defined as more than 2 mm in difference in size.

## Results

Overall, 257 (47%) of the 551 boys and 183 (41%) of the 449 girls had ventricular asymmetry. There was no significant difference in the frequency of ventricular asymmetry between the neonates born vaginally and those delivered by caesarean section ($\chi^2=0{\cdot}66$, $p>0{\cdot}05$). A total of 332 subject were scanned on the second day of life and 145 (44%) of them had ventricular asymmetry. The corresponding results for the group scanned on the third day were 153 (42%) out of 366; fourth day, 72 (47%) out of 153; and fifth day, 70 (47%) out of 149. All infants were healthy at discharge, and none had periventricular haemorrhage or other lesions detected on ultrasonography.

We observed different patterns of ventricular appearance (figure). Type 1, symmetric ventricles (boys 53%, girls 59%); type 2, wider ventricular body in one ventricle (boys 9%, girls 5%); type 3, longer occipital horn in one ventricle (boys 33%, girls 30%); type 4, both wider ventricular body and longer occipital horn in one ventricle (boys 3%, girls 3%); and type 5, either wider ventricular body with shorter occipital horn in one ventricle or vice versa (boys 2%, girls 3%). Our results are summarised in the table, which also indicates the side (left or right) in which ventricular prominence was observed.

The most common finding of ventricular difference was asymmetry of the occipital horn. A total of 249 cases (25%) (type 3, 4, and 5) showed a prominent right occipital horn, and 119 cases (12%) showed a prominent left occipital horn. In contrast, the right ventricular body was larger in 33 cases (3%) (type 2, 4, and 5), and a larger left ventricular body was noted in 91 cases (9%).

Out of a total of 440 babies with ventricular asymmetry, 428 (97%) had differences in measured

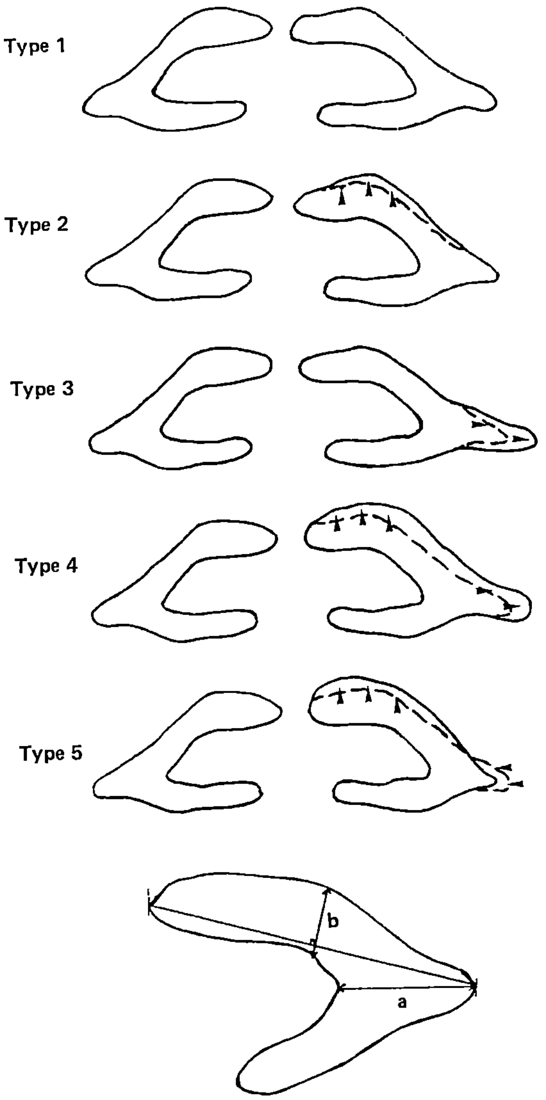

Figure *Size relationship between the lateral ventricles in the sagittal plane. Type 1, symmetric ventricles. Type 2, wider ventricular body in one ventricle. Type 3, longer occipital horn in one vehicle. Type 4, wider ventricular body and longer occipital horn. Type 5, wider ventricular body but shorter occipital horn in one ventricle or vice versa. a=Occipital horn size, b=ventricular body size.*

indices of between 2 and 5 mm, 10 (2%) had differences between 5 and 8 mm, and only two babies (<1%) had greater than 8 mm difference (9 mm and 10 mm respectively). Both these infants had asymmetry of the occipital horn.

Table *Distribution of ventricular asymmetry in normal neonates (n=1000)*

| | *No (%) of infants* | *Group with right > left* | *Group with left > right* |
|---|---|---|---|
| | *Boys* | | |
| Type 1 | 294 (53) | — | — |
| 2 | 49 (9) | 13 | 36 |
| 3 | 180 (33) | 123 | 57 |
| 4 | 15 (3) | 5 | 10 |
| 5 | 13 (2) | 2* | 11† |
| Total | 551 (100) | 143 | 114 |
| | *Girls* | | |
| Type 1 | 266 (59) | — | — |
| 2 | 23 (5) | 6 | 17 |
| 3 | 136 (30) | 94 | 42 |
| 4 | 11 (3) | 5 | 6 |
| 5 | 13 (3) | 2* | 11† |
| Total | 449 (100) | 107 | 76 |

*Wider ventricular body but shorter occipital horn on right ventricle.

†Wider ventricular body but shorter occipital horn on left ventricle.

## Discussion

The human brain is unique in the functional asymmetry that exists between its two cerebral hemispheres.[4] Anatomical studies have also shown that hemispheric asymmetry is especially found in several distinct areas.[4 5] The prevalence of ventricular asymmetry in the healthy neonates varied from 16·9% to 37·9% on neurosonography,[1 2] and occipital horn asymmetry in children was noted to be 56% by pneumoencephalography.[3] Clinicians should therefore note that ventricular asymmetry exists in the normal population and is not necessarily a pathological entity.

This study showed 47% of boys and 41% of girls with different types of ventricular asymmetry in the sagittal plane. The figures presented here may serve as a reference for further anatomical study of the brain but do not reflect the true ventricular contours. In five neonates we observed the apparently anomalous combination of a relatively small ventricular body in the sagittal plane without an increased ventricular width in the coronal plane (or the reverse). This indicates that some healthy neonates may have distorted ventricles or 'compressed lateral ventricles'.[3] A three dimensional study of the ventricles warrants further investigation with newer imaging techniques.

Among the 440 neonates with asymmetric ventricles, 341 were delivered vaginally and 99 were born by caesarean section. There was no significant difference between the mode of delivery or the age of the babies at scanning and the incidence of ventricular asymmetry. Asymmetry of brain has been found in all age groups from the fetus to the adult.[4 6] We believe that asymmetry of the lateral ventricles and probably that of the brain is influenced by genetic factors or environmental events that occur during the growth of the brain and not by the pressure effect through the birth canal.

In summary, we report four types of ventricular asymmetry based on the sonographic findings of 1000 normal Chinese neonates. Although our figures do not reflect the true ventricular contours, these findings may have some value for future studies of the neonatal brain.

The authors thank Miss Chiu-Hsiang Hsu for typing the manuscript.

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# Plasma vitamin $K_1$ concentrations in cystic fibrosis

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SUMMARY Plasma concentrations of vitamin $K_1$ were similar in 37 patients with cystic fibrosis (median 46 ng/l) and 16 controls (49 ng/l). The plasma concentrations were lower than those previously described in adults, but higher than in neonates. There was no association between an increase in prothrombin time and vitamin $K_1$ plasma concentration.

Children with cystic fibrosis suffer from malabsorption and are, therefore, prone to deficiencies of fat soluble vitamins. Clinical problems secondary to vitamin K deficiency, however, are rare in cystic fibrosis.[1] Komp and Selden reviewed 59 patients and found only four with an increased prothrombin time and possible vitamin K deficiency.[2] A subsequent study, however, measuring factor II antigen and activity suggested that vitamin $K_1$ deficiency is common in cystic fibrosis.[3]

The measurement of vitamin $K_1$ is technically difficult and there are no data on plasma concentrations in children. We therefore decided to measure plasma concentrations of vitamin $K_1$ in children with cystic fibrosis and also a group of control children.

## Patients and methods

Blood samples (5 ml) were collected from 37 patients (28 fasting) with cystic fibrosis (mean age 10·6 years, range 2–23 years) and 16 children (controls, all non-fasting) who were having venepunctures at the general outpatients' clinic (mean age 7·6 years, range 3–14 years). The children with cystic fibrosis were attending the Regional Centre at St James's University Hospital where routine annual assessment included the measurement of plasma concentrations of vitamins A and E, faecal fats, liver function tests, and prothrombin time. Plasma concentrations of vitamin $K_1$ were measured by high performance liquid chromatography coupled to dual cell electrochemical detection.[4] The limit of sensitivity for the assay was 4 ng/l. Statistical anlysis was by Spearman's rank correlation and the Mann-Whitney U Test.

Ethical approval was obtained from the local ethics committee.

## Results

The individual plasma concentrations of vitamin $K_1$ are shown in the figure. Nine children (two controls) had plasma vitamin $K_1$ concentrations below the limit of detection (4 ng/l). There was no difference in the plasma vitamin $K_1$ concentrations in the non-fasting (mean 71·1, median 45 ng/l) and fasting (mean 76·6, median 48 ng/l) patients with cystic fibrosis. Therefore, the two groups were amalgamated and the results compared with the controls. One of the children in the control group had a very high plasma concentration of vitamin $K_1$ (2115 ng/l) and was excluded when determining the mean. Although the mean plasma concentration of vitamin $K_1$ was lower in the patients with cystic fibrosis (75·2 ng/l) than in the controls (172·5 ng/l), the median values were similar (46 and 49 ng/l respectively).

Nine patients had a prothrombin time index of 1·2 or greater and their plasma concentrations of vitamin $K_1$ are shown in the figure. There was no association between a raised prothrombin time index and plasma concentrations of vitamin $K_1$ (Mann-Whitney U test, $p>0·2$).

There was no correlation between the plasma concentration of vitamin $K_1$ and age, faecal fats, plasma concentrations of vitamins A and E, or the clinical state of the patient (Shwachman and Crispin-Norman scores) (Spearman's rank correlation, $p>0·1$).

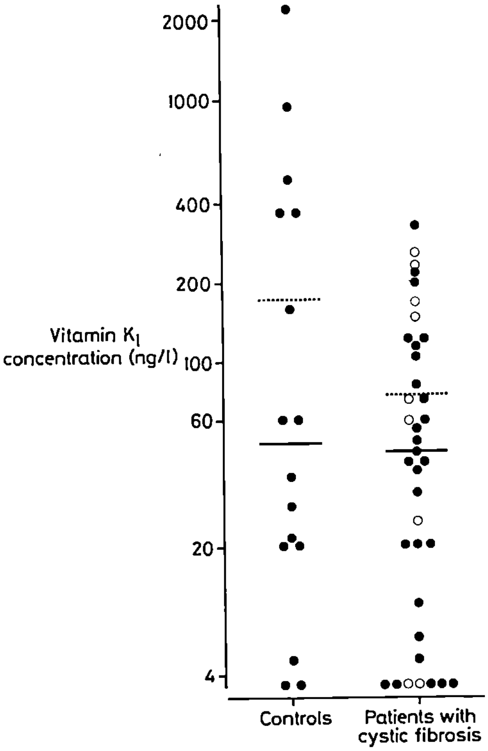

Figure *Plasma concentrations of vitamin $K_1$ in controls and patients with cystic fibrosis. Patients with prothrombin time index >1·2 are indicated by open circles. The mean (-----) and median (———) values are shown.*

## Discussion

There was considerable interindividual variation in the plasma concentrations of vitamin $K_1$. There have been no previous studies of plasma concentrations of vitamin $K_1$ in children outside the neonatal period. The concentrations detected in the control children were lower than that described in healthy adults (mean 260 ng/l, median 210 ng/l, range 100–660 ng/l)[5] and higher than that reported in newborn babies (mean 18 ng/l, median 16 ng/l, range 4–45 ng/l).[6]

Although the mean plasma vitamin $K_1$ concentration in patients was lower than that in controls, the median values were similar. Case reports of undiagnosed patients with cystic fibrosis presenting with bleeding problems describe individuals under the age of six months.[1] Our results suggest that children with cystic fibrosis of the age range studied (no infants) do not have vitamin $K_1$ deficiency.

The relationship between plasma and hepatic concentrations of vitamin $K_1$ is unknown. Neonatal hepatic concentrations of vitamin $K_1$ are significantly lower than in adults. Vitamin $K_1$ is responsible for the $\gamma$ carboxylation of clotting factors II, VII, IX, and X and the minimum plasma concentration required for adequate $\gamma$ carboxylation is unknown. The prothrombin time appears to be an inadequate marker of vitamin $K_1$ state. There was no association between prothrombin time and plasma concentration of vitamin $K_1$. The patients with an increase in prothrombin time were slightly older (mean age 12·9 years) than the group in general and it is probable that other factors are involved in causing an increase in prothrombin time.

Routine vitamin $K_1$ supplementation for patients with cystic fibrosis is not required. Further studies are required to see whether oral supplementation has any effect on those patients with an increase in prothrombin time.

We thank the nursing staff of the Regional Cystic Fibrosis Unit and Mr John Wheeldon for their help in the collection of samples. We also thank Mrs P Hibbett for typing the manuscript.

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# Water intoxication and hyponatraemic convulsions in neonates

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SUMMARY We studied two neonates fed diluted formula and excessive water who developed hyponatraemic convulsions; treatment included intravenous hypertonic saline and water restriction. Educating mothers is important to stop recurrences.

From 1967 to 1983 there were 24 cases of infants with water intoxication reported in the literature; their ages ranged from 3 weeks to 11 months.[1–4] We report two neonates with seizures secondary to water intoxication.

## Case reports

### CASE 1

A 20 day old girl, the product of a full term, normal delivery, was the first child born to a healthy 20 year old mother. The baby had been well since birth. On the day of admission she was taken to hospital because of irritability and slight abdominal distension not associated with vomiting or diarrhoea. The physical examination was unremarkable and after reassuring the mother the child was sent home. One hour later the baby had a tonic-clonic convulsion and was readmitted to hospital where she was treated with intravenous diazepam. Blood was taken for biochemical and microbiological investigations. The child was given 5% dextrose in one fifth normal saline intravenously.

Physical examination on admission (after intravenous diazepam) showed an unconscious child with a rectal temperature of 36·5°C, pulse rate 120/minute, and respiratory rate 36/minute; there was no anaemia, jaundice, or oedema. The anterior fontanelle was open and soft, the abdomen was slightly distended with normal bowel sounds, and there was no hepatosplenomegaly. The patient responded to deep pain by moving her extremities; her pupils were equal and reactive to light.

The white cell count was $5·37\times10^9$/l with 60% polymorphonuclear cells and 40% lymphocytes, and the haemoglobin concentration was 107 g/l. A microscopic examination of the urine was normal with a specific gravity of 1·005. The blood urea nitrogen was 3·2 mmol/l and the blood glucose concentration 7·8 mmol/l. The concentration of sodium in the serum was 117 mmol/l, potassium 4·8 mmol/l, chloride 92 mmol/l, and carbon dioxide 15 mmol/l. The osmolality of the serum was 240 mmol/kg and of the urine 83 mmol/kg. The cerebrospinal fluid was normal; culture of blood, urine, and cerebrospinal fluid gave negative results.

Because of the severe hyponatraemia in an otherwise healthy infant a detailed history of feeding was taken from the mother. On the day before admission the baby had been given 2 oz of diluted formula consisting of one tablespoon of S26 powdered milk (Wyeth (Ireland) Ltd) in 3 oz of water every four hours; in between each feed the mother gave the infant 4 oz of water. Throughout this period she passed a large quantity of urine. The diagnosis of hyponatraemia caused by excess feeding of water was made and the baby was managed by restricting fluid intake. No further convulsion occurred and the serum electrolytes became normal on the following day.

### CASE 2

An 8 day old boy, the fifth child of an impoverished family, was born at term after a normal vaginal delivery, weighing 3020 g. The Apgar scores were 9 and 10 at one and five minutes, respectively. The baby had no problem during his nursery stay. At home he was fed 2 oz of a normal dilution of S26 every two hours followed by 2 oz plain water. On the day of admission the baby became lethargic and fed poorly. He developed intermittent tonic-clonic seizures which lasted for three hours. In the emergency room the baby was given 15 mg phenobarbitone intravenously. His convulsions stopped but they recurred several times and could not be controlled by phenobarbitone, diazepam, calcium gluconate, or glucose.

On admission his temperature was 36°C, pulse rate 112/minute, and respiratory rate 38/minute. He weighed 3140 g. He was unconscious and was having tonic-clonic convulsions; his anterior fontanelle was slightly tense; he was not oedematous. The rest of the physical examination was normal. Laboratory investigations showed a serum sodium concentration of 116 mmol/l, chloride 86·9 mmol/l, potassium 4·99 mmol/l, carbon dioxide 16·9 mmol/l, glucose 7·2 mmol/l, calcium 2·2 mmol/l, and phosphorus 2·02 mmol/l. Culture of blood, urine, and cerebrospinal fluid gave negative results.

The seizures stopped after 20 ml of 5% sodium chloride was given intravenously; the boy had no further seizures.

## Discussion

These two infants had no history of any salt losses to account for the hyponatraemia and appeared clinically well hydrated with no evidence of oedema. From the history of excess water intake, hypothermia, low serum osmolality, low serum sodium concentration, normal serum blood urea nitrogen and creatinine we concluded that the babies had dilutional hyponatraemia after an increased water intake. Case 1 was the first child of an inexperienced mother. The second case was the fifth child of an impoverished family; water intoxication occurred because of feeding the child large amounts of water.

Most infants with water intoxication have hypothermia, are sleepy or irritable, and when seizures occur they are often multiple and recurrent. Some cases reported had oedema and hypertension; hyponatraemia with a sodium concentration of less than 125 mmol/l, a low chloride, and low carbon dioxide concentration was common. In one of our cases as well as cases reported by others,[1–4] the blood urea nitrogen was higher than the normal range for their age,[5] which might reflect a blood volume contraction due to shifting of water from the extracellular fluid to the cell when hyponatraemia occurred; the transient rise in blood glucose concentration was presumably caused by the seizures and stress.[1]

The mechanism of hyponatraemia is controversial: inappropriate secretion of antidiuretic hormone or inability of the kidney to excrete excess water have been suggested.[2] In young infants kidney function is immature, and the glomerular filtration rate is only 30% of that of a normal adult.[6] When infants ingest large amounts of water over a short period of time their kidneys are unable to excrete the large water load; this results in a dilution of their serum sodium, and salt depletion can further impair water excretion.

In the young infant with a strong sucking reflex, however, a baby might be satisfied with sucking and ingest excess water if it is continually offered by the mother. Crumpacker and Kriel theorised that infants continue to drink excess water because they are hungry.[3]

We are grateful to Dr Peter Echeverria from the United States Army Medical component Armed Forces Research Institute of Medical Sciences for revising this manuscript.

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# Respiratory muscle training in Duchenne muscular dystrophy

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SUMMARY Twenty two boys with Duchenne muscular dystrophy were entered into a randomised double blind crossover trial to compare respiratory muscle training with a Triflow II inspirometer and 'placebo' training with a mini peak flow meter. Supine posture was associated with significantly impaired lung function, but respiratory muscle training showed no benefit.

The fundamental respiratory problem in Duchenne muscular dystrophy is progressive intercostal and diaphragmatic muscle weakness often complicated by scoliosis. In practice the absolute lung volumes and forced expiratory flow measurements increase up to the age of 10–12 years, after which they fail to improve further with age, producing a fall in spirometric indices in late teenage life with deterioration in blood gas concentrations and eventual death.[1]

One potential method of improving lung function in Duchenne muscular dystrophy is respiratory muscle training. Such a method would be useful as a means of preparing the child for surgery. Martin *et al*[2] and Houser *et al*[3] have claimed benefit from respiratory muscle training, but neither used a control period of placebo training. We performed a double blind, placebo controlled, crossover study to evaluate the effect of short term respiratory muscle training on lung function.

## Patients and methods

Twenty two boys with Duchenne muscular dystrophy aged 9–14 years (mean 11·6) were recruited from two special schools where they received daily physiotherapy. They were randomised to receive either respiratory muscle training using a Triflow II Inspirometer (Cheseborough Ponds) to a total of 20 inspirations/day, or 'placebo' training using a mini peak flow meter to a total of 10 expirations/day, administered by the school physiotherapists. Triflow training entailed forced inspiration against a resistance that increased as inspiratory flow increased. Preliminary studies with other children with Duchenne muscular dystrophy showed that 20 inspirations exercised the respiratory muscles to the point of fatigue, whereas 10 forced expirations through a mini peak flow meter caused no fatigue. After 18 days using either Triflow or placebo, each child 'crossed over' to the other form of treatment for a further 18 days. An arbitrary six point scale was attached to each Triflow device so that the child's effort could be recorded. The supervising physiotherapist kept a detailed diary of the Triflow scores and the peak expiratory flow rates to ensure that each child did a comparable amount of exercise, and to look for improvements during training.

Lung function was assessed initially and at the end of each training period by two of the authors (ER, FM) who were unaware of the nature of the randomisation. Forced vital capacity (FVC), forced expiratory volume in one second ($FEV_1$) were recorded, and peak expiratory flow rate (PEFR) was measured with a pocket spirometer (Micromedical). These measurements were made in each of three positions: sitting, supine, and sitting again, to assess the effects of posture and fatigue on lung function. The best of each set of three measurements in each position was used for analysis. Predicted normal values were based on armspan.[4] Maximal inspiratory mouth pressure (PImax) was measured by a standard method,[5] and the best of three measurements used for analysis.

To compare the effect of Triflow and placebo training we applied a standard crossover analysis that permits the treatment to be compared by paired *t* test among all subjects if the order of administration does not alter the treatment effect.[6]

## Results

Of the 22 children recruited to the study two were withdrawn because of illness during the study period. Eleven children started with 'placebo' respiratory muscle training using the mini peak flow meter, and crossed over to the Triflow inspirometer during the second three week period (group 1). Nine children performed the training in the reverse order (group 2). There was a significant fall in FVC when spirometry was performed in the supine position (mean FVC 34·6% of predicted values) compared with sitting (mean FVC 38% of predicted values, $p<0·05$), but no significant change in any spirometric measurement between the two tests performed in the sitting position, indicating that the subjects were not fatigued during testing.

The scores obtained during the training periods using the mini peak flow meter and the Triflow inspirometer often improved during the first two or three days of training, but overall there were no significant improvements in scores during either of the training periods in both group 1 and group 2 children.

The results of the lung function tests before and after the training periods are given in table 1. There were no significant changes in FVC or $FEV_1$ during either placebo training or Triflow training for either group of children when compared with baseline data. Group 1 children (who received placebo training before Triflow) showed significant improvements in PEFR during the placebo training period ($p=0·02$), but not during Triflow training. The same tests used to compare baseline data with Triflow training showed a significant change in PImax values ($p=0·02$), which suggests a strong learning effect during the study. The standard analysis for crossover designs for determining the effect of Triflow compared with placebo training showed no significant differences for any of the measurements (table 2, column 4),[6] nor did the order in which the treatments were given affect the results (table 2, column 3).

## Discussion

Considering the design of this study we presume that the Triflow Inspirometer exercises the diaphragm, which is the most important muscle of respiration,

Table 1 *Mean (SD) lung function tests measured in the sitting position before and after respiratory muscle training periods*

| *Group 1 (n=11)* | | | | *Group 2 (n=9)* | | | |
|---|---|---|---|---|---|---|---|
| *FVC* | *$FEV_1$* | *PEFR* | *PImax* | *FVC* | *$FEV_1$* | *PEFR* | *PImax* |
| Baseline measurement | | | | Baseline measurement | | | |
| 1·30 (0·51) | 1·20 (0·46) | 163* (65) | 49 (21) | 1·58 (0·53) | 1·50 (0·53) | 209 (75) | 43† (21) |
| Period 1 (after placebo training) | | | | Period 2 (after Triflow training) | | | |
| 1·34 (0·60) | 1·29 (0·56) | 194* (69) | 60 (29) | 1·50 (0·48) | 1·47 (0·48) | 226 (59) | 62† (16) |
| Period 2 (after Triflow training) | | | | Period 2 (after placebo training) | | | |
| 1·31 (0·55) | 1·24 (0·49) | 188 (76) | 61 (24) | 1·58 (0·53) | 1·55 (0·51) | 240 (60) | 75 (23) |

* and †: p=0·02.

Table 2 *Mean measurements of lung function measured in the sitting position, during either placebo training or respiratory muscle training using a Triflow inspirometer, to show the effect of treatment*

| | *After placebo training* | *After Triflow training* | *Difference (placebo-Triflow) for each group* | *Mean (SE) Triflow effect for all 20 patients* |
|---|---|---|---|---|
| **FVC** | | | | |
| Placebo training first (n=11) | 1·34 | 1·31 | 0·03 | |
| Triflow training first (n=9) | 1·58 | 1·50 | 0·08 | 0·05 (0·07) |
| **$FEV_1$** | | | | |
| Placebo training first (n=11) | 1·29 | 1·24 | 0·05 | |
| Triflow training first (n=9) | 1·55 | 1·47 | 0·08 | 0·06 (0·07) |
| **PEFR (l/min)** | | | | |
| Placebo training first (n=11) | 194 | 188 | 6·0 | |
| Triflow training first (n=9) | 240 | 226 | 14·0 | 9·6 (6·7) |
| **PImax (cm $H_2O$)** | | | | |
| Placebo training first (n=11) | 60 | 61 | − 1·0 | |
| Triflow training first (n=9) | 75 | 62 | 13·0 | 5·3 (4·4) |

whereas the peak expiratory flow meter exercises the muscles of the abdomen and other accessory muscles, which are less important. In their study of training Martin *et al* claimed to show improvement of muscle endurance,[2] but the clinical value of this is uncertain. The vital capacity is possibly the best index of lung function as it has been repeatedly shown to predict both survival, and the ability to withstand spinal surgery without respiratory complications.

In this study we have attempted to eliminate bias in lung function testing by a double blind placebo design. When learning effects are allowed for, this study does not convincingly show any improvement in lung function from short term respiratory muscle training. It is important to note that lung function is significantly worse in the supine position—a factor likely to be relevant in postoperative care.

We thank Mrs J Perk, physiotherapist, and the pupils of the Lord Mayor Trealors School, Alton, and Mrs J Breese, physiotherapist, and pupils of Sherbourne School, Coventry, for their help and enthusiasm in completing this study. Our muscle research programme is supported by a centre grant from the Muscular Dystrophy Group of Great Britain.

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# Congenital tuberculosis localised to the ear

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SUMMARY We report two infants who had localised congenital tuberculous otitis. In both cases the infants presented with an ear discharge and both mothers had been diagnosed as having miliary tuberculosis. Infection is thought to have occurred in utero or during birth.

Congenital tuberculosis is seldom reported, and when it occurs it tends to be a multisystem disorder with a poor perinatal outcome.[1–3] In older children isolated tuberculous otitis is well described[4 5]; isolated congenital tuberculosis of the ear, however, has not been previously reported.

## Case reports

### CASE 1

A boy, weighing 670 g, was born vaginally at 27 weeks' gestation. The mother, a 27 year old primigravida, had booked at 14 weeks. At 23 weeks she was admitted for minor antepartum haemorrhage and unexplained fever. There were no respiratory symptoms. Several blood and urine cultures were negative. A fluctuating temperature persisted despite treatment with paracetamol, indomethacin, and co-trimoxazole. Eight days before delivery, on radiological evidence, a diagnosis of miliary tuberculosis was made and treatment was started with isoniazid, ethambutol, rifampicin, and pyrazinamide. Despite indomethacin and hexoprenaline suppression, spontaneous premature labour and delivery ensued.

Histological examination of the placenta showed small areas of infarcted villi with associated haemorrhage and fibrin deposits on maternal surfaces. Areas of caseous necrosis were noted (figure). Numerous acid-alcohol fast bacilli were seen on Ziehl-Nielsen staining. This information was, however, only discovered after discharge of the infant.

Immediately after delivery the infant was taken to the neonatal intensive care unit. He had clinical and radiological features of hyaline membrane disease, but required headbox oxygen only. Apnoeic spells occurred from days 15 to 45. Investigations for sepsis and metabolic abnormalities were negative,

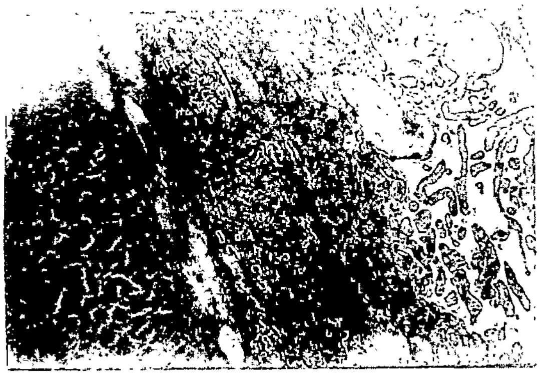

Figure *Photomicrograph of placental tissue showing normal villi on the right and caseous necrosis of placenta on left. (Haematoxylin and eosin stain×5000.)*

and chest radiographs were clear. The infant thrived. BCG was not given at birth, in accordance with routine nursery practice not to administer BCG at discharge to premature infants.

A whitish seropurulent discharge of the infant's right ear was noted on day 68 (when he weighed 1650 g); a pus swab of the discharge grew *Proteus mirabilis*. An otorhinolaryngologist prescribed dry mopping, amoxacillin orally, and framycetic sulphate eardrops locally. Twelve days later (day 88) progressive right preauricular and upper cervical lymphadenopathy became apparent. The aural discharge persisted. In view of the duration of the otitis and the perinatal history, the diagnosis of tuberculous otitis was considered; and at repeat otoscopy a granuloma was removed from the auditory canal.

Histology showed acutely inflamed granulation tissue, with epitheloid granuloma; acid-alcohol fast bacilli were shown. Multiple drug treatment was commenced (isoniazid, rifampicin, ethambutol, and pyrazinamide). Systemic examinations throughout his hospital stay and after discharge, on days 95 and 125, were normal as were the chest radiographs. By day 150 the aural discharge had cleared and lymphadenopathy was appreciably reduced. The infant was thriving and had normal developmental milestones.

### CASE 2

A boy, weighing 1560 g, was born vaginally at an estimated 36 weeks' gestation. After four uneventful weeks in the nursery the infant was discharged well and weighing 2100 g. BCG immunisation was given before discharge.

One week later the mother presented with cough, chest pain, and night sweats, of two weeks' duration. Miliary tuberculosis was diagnosed on the basis of a typical chest radiograph, though her sputum was negative for acid-fast bacilli.

On admission, the mother stated that her baby had had a discharging left ear for four days, but had been otherwise well. Examination of the baby showed firm, non-tender, left sided periauricular lymphadenopathy. Otoscopy showed friable granulation tissue and thin pus filling the auditory canal. Microscopy showed moderate acid-alcohol fast bacilli, but culture for acid-fast bacilli was negative. No other pathogens were cultured. A chest radiograph was normal, and Mantoux test negative. Based on maternal history, clinical features, and pus microscopy, a diagnosis of tuberculosis was made. Quadruple chemotherapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) was commenced.

At 3 months, the infant was thriving, with reduction in lymphadenopathy and aural discharge. Systemic examinations were normal throughout. Investigations for tuberculosis at other sites were negative.

## Discussion

Congenital tuberculosis, although rare, still occurs sporadically and is preventable.[1–3] The fetus and newborn infant are susceptible to several potential routes of infection: directly via placental circulation by in utero aspiration of infected amniotic fluid, or in the case of maternal genital tuberculosis, at birth during descent through the birth canal.[3]

The clinical presentation and diagnosis of congenital tuberculosis has recently been well summarised by Bate *et al.*[6] In recent English language literature, congenital tuberculosis with otitis has been reported, but all these patients had systemic involvement.[1 2] Aural discharge as a presenting sign of tuberculosis in early infancy has also been reported,[4 5] but it is not clear whether infection was acquired congenitally or postnatally.

Our patients were unusual in that they showed no signs of systemic infection either before or up to five months (case 1) and three months (case 2) after diagnosis and initiation of treatment. Investigations for tuberculosis at other sites were consistently negative. Both infants have thrived, in contrast with the usual perinatal outome of congenital tuberculosis.

The mother of our first patient had no respiratory symptoms, had been on antituberculous treatment from eight days before delivery, and was considered to be non-infectious at the time of handling her baby. Although she visited regularly, her infant was in an incubator for many weeks and she only cuddled him later on. The infant is therefore presumed to have been infected in utero.

Although the second infant was home for seven days before the mother's diagnosis, it is unlikely that this infant was infected postnatally, as this period was considerably less than the six to eight weeks required by the tubercle bacilli to multiply.

The ear would be a most unusual site for a primary infection. It is speculated that transmission occurred by infected amniotic fluid being lodged in the fetal auditory canal, either in utero or during birth. After birth, the auditory canal provides a moist, relatively well oxygenated environment suitable for growth of tubercle bacilli. The delay in clinical presentation accords well with the time required by the organism to multiply. The absence of systemic manifestations make infection from transplacental spread, or by aspiration of infected liquor, unlikely.

We thank Dr NT von Diggelen for interpretation of the histology and photographs, and Drs JD Kane-Berman (Groote Schuur Hospital) and Frazer-Ross (Brooklyn Chest Hospital) for permission to publish.

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# Munchausen's syndrome in a 4 year old

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SUMMARY From the age of 4 a boy repeatedly feigned epileptic fits. He later admitted that his mother had taught him that he was epileptic and had trained him to behave like that.

Munchausen's syndrome by proxy is the fabrication by a mother of false symptoms and signs of illness in her child. The commonest form of this syndrome is fictitious epilepsy. We describe a case where a mother not only fabricated a false history of epilepsy in her 4 year old son, but also trained him to feign epileptic fits.

## Case report

A 2 year old boy was referred to the outpatient department by his family doctor because his mother had reported that he had episodes of cyanosis. No abnormality was found. He was again referred at the age of 3 because of episodes of shaking and unconsciousness. The electroencephalogram was normal, and no firm diagnosis was made. His mother continued to report that he had fits and when he was 4 years old a diagnosis of epilepsy was made and he was treated with sodium valproate. Three months later he was admitted to hospital because of fits, and on several occasions was observed lying apparently unconscious and trembling. He was, however, easily roused by the mention of his favourite food, and it was obvious that he was feigning the fits. The diagnosis of epilepsy was withdrawn and treatment was stopped.

His mother continued to claim that he was having fits, and so they were both referred for psychiatric help. Despite this she repeatedly brought him to hospital claiming he had been having fits. On one occasion he was brought to the clinic in a pushchair, wearing nappies and a crash helmet, and being fed from a baby's bottle. When he was 5 he was admitted to hospital during an apparent fit, and was given intravenous diazepam by a house officer who did not know him. During this admission he feigned further fits, and pretended to have a paralysed arm for two days. He also stated that he was epileptic. Two weeks later he was again admitted to hospital during an apparent fit but the next day was able to give a clear account of all that had occurred at that time.

At a case conference the family doctor told us that the boy had been brought to the surgery 130 times.

This was in addition to 35 visits to the hospital accident and emergency department. During this conference, the head teacher of the boy's school recounted conversations between herself and the boy that she had recorded on tape. He had described how his mother had trained him to simulate epileptic fits by falling off his chair, shivering, and flickering his eyes. He had been seen to act in this way at school, and had told his head teacher that he had done so 'because mummy said I should'. He also told her that his mother sometimes rewarded him with food and drink when he had acted in this manner. The head teacher said that for a child of his age his ability to express himself was exceptional, and that his statements were clear and unambiguous.

The decision of the case conference was that an application should be made to the Court for the boy to be taken into care. Five months after being received into care, the boy had had no further fits. He told our child psychiatrist that he no longer had epilepsy.

## Discussion

We have described a boy whose mother not only claimed that he was epileptic, but also trained him to feign epileptic fits from the age of 4½.

Fictitious epilepsy is the commonest form of Munchausen's syndrome by proxy.[1] The parent, invariably the mother, attempts to convince doctors that her child has epilepsy. The commonest strategy is simply to give an untruthful history. A second less common strategy is to induce fits in the child, usually by smothering.[2] This sometimes occurs in hospital, and has been detected by video surveillance.[3] This case shows that a third strategy may be adopted: to train the child to feign epileptic fits. This strategy has not previously been reported to our knowledge.

This case has many typical features of Munchausen's syndrome by proxy. There are also some features of classical Munchausen's syndrome: the child himself feigned illness, and claimed to be suffering from this illness, admittedly because his mother had trained him to do so. Munchausen's syndrome has not previously been described in a child of this age. According to Meadow, in cases of Munchausen's syndrome by proxy it is quite common to find that as the child reaches school age complicity develops between the mother and child, and that 'the fabrication becomes a joint effort'.[2] Later, older children may be 'programmed into illness behaviour'. We can find no previous report of a child having been successfully 'programmed into illness behaviour' at the age of 4.

The diagnosis of fictitious epilepsy may be difficult and is often delayed. In the series reported by Meadow the median length of the false illness was 3·9 years. Many of these children may have been too young to give a history themselves. Nevertheless our case shows that in fictitious epilepsy, as in other forms of child abuse, an interview with the child can yield important information.

We thank Dr K Norton for permission to report one of his patients.

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742 *Archives of Disease in Childhood,* 1989, **64**

# 2 Year old asthmatics can learn to operate a tube spacer by copying their mothers

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SUMMARY The mothers of 20 asthmatic children aged between 1·9 and 2·9 years were taught to use a tube spacer; 15 (75%) succeeded in teaching their children to operate it. Eight children (40%) inhaled salbutamol correctly. Inability to tolerate salbutamol was as common as failure to use the spacer correctly.

Preschool children with asthma can use tube spacers effectively.[1 2] Although Warner has stated that most children over the age of 2 can learn to use a tube spacer,[3] there have been no reports confirming the correct use of these devices by 2 year old children. I reviewed my experience of teaching mothers to teach their 2 year old asthmatic children to use a tube spacer.

## Patients and methods

Over a three month period, 20 consecutive asthmatic children aged between 1·9 and 2·9 years (mean 2·3) attending hospital as outpatients were given a tube spacer (Volumatic). This is a plastic cone, similar in design to the Nebuhaler, with a mouthpiece containing a valve at one end and an aperture at the other through which salbutamol can be sprayed from a metered-dose inhaler. The mother of each child was taught to operate the tube spacer and then asked to teach her child at home. The principle was that children should learn by copying their mothers. No attempt was made by hospital staff to instruct the children directly.

Children were reviewed as outpatients for up to two months. When a child had learned to operate the tube spacer correctly, a salbutamol metered dose inhaler was prescribed. The mother was asked to give salbutamol at home if the child had symptoms of asthma.

The children's ability to operate the tube spacer and to inhale salbutamol was assessed by a paediatrician in the outpatient department. The correct method of operating the tube spacer was defined as the ability to take five consecutive breaths sufficient to open and close the valve.[4] Correct inhalation of salbutamol was defined as the ability to perform this manoeuvre after a puff of salbutamol had been sprayed into the spacer.

## Results

Fifteen of the 20 children learned to operate the tube spacer correctly. Some of them grimaced, however, when given salbutamol, and would not continue inhaling it after one or two breaths (table). Two of this group also coughed while inhaling salbutamol, and two said that they did not like it. Five other children also coughed while inhaling salbutamol, but were able to finish inhaling it correctly.

## Discussion

Most of the mothers were able to teach their 2 year old children to operate the tube spacer correctly in the manner described by Gleeson and Price.[4] This method of teaching children is simple, effective, and has not previously been emphasised. It only takes a few minutes to teach a mother to use a tube spacer, and there is no need to refer children to a physiotherapist for instruction, as is the practice in many hospitals. Most of the children attempted to take the tube spacer from their mother as soon as they saw her using it. Many children therefore began using the spacer immediately, and subsequently perfected their technique at home.

Unfortunately some of the children who were able to operate the tube spacer correctly found salbuta-

Table *Ability of 2 year old asthmatics to tolerate salbutamol inhaled from a tube spacer*

| | *No of children* | *Mean age (years)* |
|---|---|---|
| No able to tolerate salbutamol | 8 | 2·3 |
| No unable to tolerate salbutamol | 5 | 2·7 |
| No lost to follow up | 2 | 2·4 |
| Total No able to operate spacer | 15 | 2·3 |

most distasteful and refused to inhale. Failure to tolerate inhaled salbutamol was as common as failure to learn to operate the tube spacer correctly. It is not clear whether salbutamol, or some other component of the aerosol, is specifically unpalatable to children, or whether young children are simply apprehensive at being asked to inhale an unfamiliar substance. This question merits further investigation.

This study does not set out to show that β adrenergic stimulants inhaled in the manner described will produce bronchodilation in 2 year old asthmatics; this has already been shown, albeit in a slightly older group of children (mean age 3·6 years).[5] The results do suggest, however, that tube spacers can be prescribed for 2 year old asthmatics with a reasonable expectation that they will use them correctly.

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# Reactive arthritis complicating cryptosporidial infection

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SUMMARY Two cases of reactive arthritis in association with cryptosporidial enteritis in childhood are reported. Oocysts of cryptosporidium should be sought when arthritis complicates diarrhoeal illnesses.

The coccidian parasite cryptosporidium is a common cause of gastrointestinal infection in childhood.[1] In the west of Scotland it is the commonest identified cause of gastroenteritis in children.[2] In immunocompetent subjects the disease is self limiting and there is no satisfactory treatment. The symptoms comprise diarrhoea without bleeding, abdominal pain, vomiting, and sometimes fever. Various complications have been described including prolonged listlessness, lethargy, loss of appetite, and failure to thrive.[2] We know of only one previous report of reactive arthritis, which occurred in an adult.[3] We report here two cases of reactive arthritis associated with cryptosporidial infection in childhood.

## Case reports

### CASE 1

A 3½ year old girl whose mother ran a riding school was admitted to hospital with a week's history of vomiting and diarrhoea. She had become lethargic and had developed swollen, cold, blue, painful feet on the day of admission. On admission she was flushed and feverish and had cold swollen feet. The next day she was not keen to bear weight and had developed swollen, warm, tender ankles with similar changes in the wrists, but to a lesser degree. Her haemoglobin concentration was 151 g/l, white cell count $16\times10^9$/l, and erythrocyte sedimentation rate 27 mm in the first hour. Blood cultures, throat swab, and urine culture grew no pathogens. Stool culture and serology for rotavirus, rheumatoid factor, and campylobacter showed no abnormalities. Oocysts of cryptosporidium were seen on microscopy of the stool. She was treated initially with clear fluids orally followed by a return to a normal diet, but loose stools and fever continued for several days. The warm, tender, swollen ankles and wrists persisted for four days after admission and she was reluctant to bear weight for a total of 10 days; thereafter she made a spontaneous recovery and was discharged home.

### CASE 2

A 5 year old girl was admitted to hospital with a five day history of severe diarrhoea with mucus but no blood, vomiting, abdominal pain, and fever (maximum temperature 39°C). On the sixth day the index finger of her left hand became swollen, red, hot and tender at the proximal interphalangeal joint. Her haemoglobin was 148 g/l and white cell count $125\times10^9$/l. Blood cultures and stool cultures grew no pathogens but oocysts of cryptosporidium were identified in the stools. She was treated with intravenous fluids followed by a return to a normal diet.

While awaiting the results of the cultures she was given chloramphenicol and fusidic acid but this was stopped when the oocysts were identified and no further treatment was given. The joint inflammation and tenderness resolved over six days, but the diarrhoea persisted for 25 days.

## Discussion

Reactive arthritis is an occasional complication of infection by a number of bowel pathogens including salmonella, shigella, *Yersinia enterocolitica,* and *Campylobacter jejunii.*[4] The single previous report in association with cryptosporidium infection was of a 27 year old man who had widespread severe arthralgia and required aspiration of an effusion of his knee and an intra-articular injection of steroid. Mild arthralgia persisted for at least four months. He was stated to have been well before the onset of infection. He had normal immunoglobulin concentrations and did not seem to have been immunocompromised. Neither of the children reported here were immunocompromised. Compared with the adult case the two children were relatively mildly affected both in severity and duration of the disease. In neither the adult nor the two children were the mucus membranes affected. It is clear from these reports that infection with cryptosporidium must be considered not only in acute gastroenteritis but also in reactive arthritis complicating gastrointestinal symptoms.

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## *Current topic*

# Recent developments in the diagnosis and management of neurofibromatosis

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The last decade has seen increasing awareness of the problems encountered in diagnosis and management of the different forms of neurofibromatosis.[1 2] Modern techniques of clinical and laboratory investigation have been applied to the disease, culminating in 1987 with the mapping of the genes for type 1[3 4] and type 2[5 6] neurofibromatosis to chromosomes 17 and 22 respectively. In the short term this means closely linked DNA markers can be used for prenatal and presymptomatic diagnosis and in the long term the cloning of the actual genes will be a major step towards our understanding of the pathogenesis of and possible treatments for the two main types of neurofibromatosis.

## Nomenclature

Riccardi has suggested that there may be seven or more different forms of neurofibromatosis.[2] One of the problems addressed by the 1987 National Institutes of Health (NIH) Consensus Development Conference on Neurofibromatosis was that of nomenclature and classification.[7] The consensus panel concluded that at the present time there is sufficient evidence to clearly distinguish neurofibromatosis type 1 (previously known as von Recklinghausen or peripheral neurofibromatosis) and type 2 (bilateral acoustic or central neurofibromatosis). The diagnostic criteria for both type 1 and 2 agreed by the consensus panel are shown in table 1. The panel acknowledged previously reported cases with atypical features that would not have type 1 or type 2 by these criteria but clearly have a form of neurofibromatosis. It was felt that at the present time there was insufficient data available to justify further subclassification.

## Neurofibromatosis type 1

Neurofibromatosis type 1 is the commonest form of neurofibromatosis accounting for over 90% of all cases. A recent population survey in south east Wales found a prevalence of 1/4950 ($20/10^5$) of population,[8] although the actual birth incidence may be as high as 1/2500 ($40/10^5$).[9 10] Inheritance is autosomal dominant with approximately 50% of cases representing new mutations.[9 10] Gene penetrance, in offspring of individuals with well characterised type 1, is virtually 100% by the age of 5 years.[10 11]

### DIAGNOSTIC FEATURES

The diagnostic criteria for neurofibromatosis type 1 are shown in table 1. The NIH Consensus statement draws attention to distinguishing patients with McCune-Albright (polyostotic fibrous dysplasia, irregular skin pigmentation and sexual precocity)

Table 1 *Diagnostic criteria for neurofibromatosis type 1 and type 2*[7]

**Neurofibromatosis type 1**

The diagnostic criteria are met in an individual if two or more of the following are found:

≥6 Café au lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals

≥2 Neurofibromas of any type or one plexiform neurofibroma

Freckling in the axillary or inguinal regions

Optic glioma

≥2 Lisch nodules (iris hamartomas)

A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis

A first degree relative (parent, sibling, or offspring) with type 1 by the above criteria

**Neurofibromatosis type 2**

The criteria are met by an individual who has:

(1) Bilateral eighth nerve masses seen with appropriate imaging techniques (for example, computed tomography or magnetic resonance imaging)

or

(2) A first degree relative with type 2 and either: (a) unilateral eighth nerve mass or (b) two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity

and Watson syndrome (café au lait spots, dull intelligence, and pulmonary stenosis) when applying these criteria.

The major defining features of the disease are café au lait spots, peripheral neurofibromas and Lisch nodules. Café au lait spots are the first disease feature to develop and are obvious on naked eye examination by the end of the first year of life in most cases. In fair skinned people they may be extremely pale and examination is aided by the use of a Wood's lamp. The other form of characteristic skin pigmentation is axillary freckling, seen in two thirds of affected people[8] and which develops in middle childhood.

Peripheral neurofibromas, which may be cutaneous or subcutaneous, begin to appear around the onset of puberty in most cases; the youngest child the author has seen with these lesions was 6 years old. Although Lisch first described pigmented nodules of the iris in neurofibromatosis type 1 sufferers in 1937,[12] their exact frequency and diagnostic value has only recently been appreciated.[13 14] Although occasionally visible to the naked eye they are best seen by slit lamp examination. They have a characteristic dome shaped appearance, are usually brown in colour, although they can be pale or almost white in young children. Lisch nodules are present in over 90% of type 1 sufferers by the age of 5 years.

There are two minor features of neurofibromatosis type 1, which although not specific enough for diagnosis, are present in a large proportion of affected individuals. These are macrocephaly and short stature. In the Welsh study, 45% of those affected had a head circumference at or above the 97th centile and 34% had heights at or below the 3rd centile.[8] The standard deviation from normal for height for affected patients was −1·20 (1·07) in affected individuals compared with −0·12 (1·02) in normal siblings ($p=0{\cdot}001$).

The diagnosis of neurofibromatosis type 1 is usually straightforward; the only problem arises in assessing young children with multiple café au lait spots as their only feature and whose parents are unaffected. Although type 1 is likely the diagnosis cannot be made until other features develop, as families have been reported with café au lait spots alone segregating as a dominant disorder.[2 15] In this context slit lamp examination to look for Lisch nodules can be helpful, as they are usually present before axillary freckling or peripheral neurofibromas.

### COMPLICATIONS

The complications of neurofibromatosis type 1 can affect any of the body systems, and as their occurrence cannot be predicted even within families it is this aspect of the disease that is most distressing. The most frequent complications of type 1 in the Welsh study are shown in table 2.[8] The other complications seen in the study population were delayed puberty (2%), hypsarrhythmia (1%), meningioangiomatosis (1%), congenital glaucoma (1%), and bony defect of the lambdoidal suture (1%). Four previously recognised complications of type 1 were not seen in the study population even though these are part of the range of the disease: these are sphenoid wing dysplasia, pseudoarthrosis of the radius or ulna, or both, arterial disease other than renal artery stenosis, and atypical forms of childhood leukaemia. It must be assumed that their occurrence is rare in neurofibromatosis type 1 sufferers (≤1%).

The age range of presentation of type 1 complications (unless obvious) is also shown in table 2,[16] and this can be used in planning patient follow up, both for reassurance (for example, the parents of a child with no complications at 5 years can be reassured that the child will not develop a facial plexiform neurofibroma or pseudoarthrosis) and in monitoring for complications which may yet occur.

At the present time there are insufficient data for many of the complications to define an exact age range of presentation. This will only become possible when large cohorts of children with neurofibromatosis type 1 are followed up from childhood. From such studies clinical features may emerge that predispose to some complications, such as peripheral nerve malignancy, thus highlighting a subset of patients which require closer monitoring.

### MANAGEMENT

One of the problems with neurofibromatosis type 1 is that because the disease complications are so varied patients may present to many different specialists during their life and yet find no one doctor keeping an overview of their disease. In the Welsh study only 28 out of 135 (21%) of the type 1 sufferers were being regularly reviewed for their disease and this was because of complications in 16 of the 28.[8] The remaining 12, eight of whom were children, were being monitored regularly for the development of complications. Only 10 individuals had received formal genetic counselling. Many parents had been told the café au lait spots were 'just birth marks' and were unaware that subsequent problems (for example, educational difficulties, scoliosis) were related. There is therefore a need for improved patient care in neurofibromatosis type 1. Although many complications are individually rare, their combined burden is appreciable and it is likely that sufferers are not being diagnosed sufficiently early, nor receiving appropriate follow up and counselling.

Table 2 *Frequency of complications of neurofibromatosis type 1 in a population based study in south east Wales.*[8, 16] *The age range at which these can occur is also presented (unless obvious)*[16]

| *Complication* | *Frequency (%)* | *Age range of presentation (years)* |
|---|---|---|
| Plexiform neurofibromas: | | |
| All lesions | 26·7 | 0–18 |
| Large lesions of head and neck | 1·2 | 0–1 |
| Intellectual handicap: | | |
| Severe | 0·8 | |
| Moderate | 2·4 | |
| Minimal/learning difficulties | 29·8 | |
| Epilepsy: | | |
| No known cause | 4·2 | Lifelong* |
| Secondary to disease complications | 3·1 | |
| Tumours of the central nervous system | 1·5–2·2% | Optic gliomas: 0–20<br>Other tumours (usually astrocytomas): lifelong |
| Spinal neurofibromas | 2·1 | Lifelong |
| Aqueduct stenosis | 2·1 | 0–30 |
| Malignancy with established disease association: | | |
| Rhabdomyosarcoma | 1·5 | Lifelong† |
| Peripheral nerve malignancy | 1·5 | Lifelong |
| Scoliosis: | | |
| Requiring surgery | 5·2 | 0–18 |
| Less severe | 6·3 | |
| Pseudoarthrosis of tibia and fibula: | | |
| Resulting in non-union and eventual amputation | 2·1 | 0–5 |
| Less severe forms | 1 | 0–5 |
| Gastrointestinal neurofibromas | 2·1 | Lifelong |
| Renal artery stenosis | 2·1 | Lifelong |
| Endocrine tumours (phaeochromocytomas and/or duodenal carcinoid) | 3·1 | From 10 years onwards |

*'Lifelong' indicates cases have been reported presenting in all age groups.

†Although 'lifelong' risk given there is strong evidence for a subset of cases presenting with pelvic rhabdomyosarcomas in early childhood.[17, 18]

The NIH Consensus Development Conference addressed these problems and recommended that neurofibromatosis type 1 sufferers should have an annual clinical assessment to monitor for complications. It was felt that screening investigations, such as cranial computed tomography, were not justified unless there were clinical indications. As many of the disease complications develop in childhood it is this author's present practise to recommend biannual review for children. Examination should be geared to monitoring for development of complications, therefore paying particular attention to blood pressure measurement and to examination of the spine and nervous system (particularly for signs of an optic glioma). As educational problems are so frequent a preschool psychological assessment seems appropriate.

There is no specific treatment for neurofibromatosis type 1 and most complications are managed in exactly the same way as when they occur in isolation. Plexiform neurofibromas, which are rarely seen as isolated lesions, are one of the most frequent complications and present a difficult management problem. They present as diffuse ill defined swellings often with overlying skin hypertrophy or pigmentation. As their margins are ill defined complete surgical removal is often impossible. Therefore unless these lesions are causing severe cosmetic problems or localised bony overgrowth conservative management is advisable.

Mast cells are a major component of both discrete peripheral and plexiform neurofibromas. Riccardi has postulated that they may play an important part in the pathogenesis of these lesions.[15] In a recent paper, Riccardi describes possible control of the growth of aggressive plexiform neurofibromas and neurofibroma associated pruritus by the use of the drug ketotifen, which blocks mast cell secretions.[19] The trial had an open label protocol, however, and involved a small number of patients, therefore larger double blind studies are necessary before firm conclusions can be drawn.

Families who are keen to gain more information about the disease and meet other sufferers may benefit from being put in contact with the British neurofibromatosis patients association, LINK (Lets increase neurofibromatosis knowledge).*

The mapping of the gene to chromosome 17 by family linkage studies has laid open the way to applying more complex molecular techniques to clone the gene itself. Clinicians can help in this research by looking for abnormalities of chromosome 17 in unusual cases—for example, with particularly severe intellectual handicap, dysmorphic features, or more than one genetic disease. It is also now possible to examine whether the mechanism of tumour formation in neurofibromatosis type 1 is similar to that in type 2.[5] It is therefore helpful if a portion of any tumour removed from patients with neurofibromatosis type 1 can be preserved for DNA analysis.

### GENETIC COUNSELLING

Genetic counselling is an integral part of the care of neurofibromatosis type 1 sufferers and their families. The 50% risk of transmission to offspring is straightforward. It is more difficult to convey the risk of complications in offspring. There is a fine balance between providing adequate information without causing unnecessary alarm. In counselling families the author has found it useful to divide the complications into groups that focus on the effects a given complication would have on an individual's life. There are (1) intellectual handicap: moderate to severe: 2%, minimal intellectual handicap or learning difficulties: 15%; (2) complications that develop in childhood causing lifelong morbidity (severe head and neck plexiform neurofibromas, orthopaedic problems): 4%; (3) complications that can occur at any time but are 'treatable' (for example, epilepsy, endocrine tumours): 8%; and (4) central nervous system and malignant tumours: 2–3%. The frequencies for each group are taken from the Welsh study and have been halved to account for dominant inheritance and rounded to the nearest whole number.[8]

Approximately 50% of all cases of neurofibromatosis type 1 are new mutations. Before parents of an apparently isolated care are fully reassured as to their own recurrence risks, however, it is important they have a detailed cutaneous and slit lamp examination. There have been several cases reported where patients with limited disease features have had affected children.[11] For example, Riccardi and Lewis have reported a case where a mother of two affected children had bilateral Lisch nodules as her only feature.[11]

Since the mapping of the gene for neurofibromatosis type 1 to chromosome 17 in 1987 there has been rapid progress. Linkage studies of chromosome 17 markers in large numbers of families have shown no evidence of non-allelic genetic heterogenity—that is, there is no evidence for a second type 1 locus not on chromosome 17.[20] There are now several DNA markers that can be used for prenatal diagnosis with an accuracy of >95%.[21] As their clinical application will depend on a 'gene tracking' approach,[22] however, it will be limited to families with more than one affected individual who are 'informative' for the marker polymorphisms. A more widely applicable DNA or biochemical marker for neurofibromatosis type 1 will only become available with the cloning of the gene itself.

## Neurofibromatosis type 2

The diagnostic criteria for neurofibromatosis type 2 are shown in table 1. This form of neurofibromatosis has been recently comprehensively reviewed elsewhere.[23] Type 2 is much rarer than type 1 with an estimated prevalence of 1/50 000, inheritance is also autosomal dominant. The main features of neurofibromatosis type 2 are bilateral acoustic neuromas, which occur in over 95% of patients. Other tumours of the nervous system, particularly schwannomas and meningomas are often associated.

Patients with neurofibromatosis type 2 do, however, have a few café au lait spots (but always fewer than six) or peripheral neurofibromas more frequently than the general population,[24] and in the past the two forms of the disease were not clearly distinguished. Recent large surveys of type 1 sufferers have shown no increased frequency of acoustic neuromas.[8 13]

Neurofibromatosis type 2 does not usually present in childhood: the mean (SE) age of onset of symptoms from acoustic neuromas was 20·4 (1·1) years in one large series.[24] Cases have been reported with an earlier presentation, however, and the diagnosis should be considered in children presenting with meningeal or Schwann cell tumours in any location. In these cases the finding of lens opacities on slit lamp examination would make the diagnosis of neurofibromatosis type 2 a strong possibility.[23]

Genetic counselling is also important for type 2 sufferers and their families. As most gene carriers develop acoustic neuromas, screening for their development is justified[23]; surgery on small tumours at an early stage in their development is associated with the preservation of hearing in some cases and a noticeable decrease in other complications. A closely linked chromosome 22 DNA marker has been identified for neurofibromatosis type 2.[25] As the linkage studies have only been done in one large family, however, heterogeneity, although unlikely, remains a possibility and the accuracy of the marker is not yet sufficiently defined for clinical application.

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## Neurofibromatosis clinics

Several centres in the United States have now established multidisciplinary neurofibromatosis clinics,[15] with a view to improved coordination of care particularly for neurofibromatosis type 1 sufferers. There is a need for other countries to consider following this model so that expertise can be developed in treating some of the more difficult complications that are individually rare (for example, facial plexiform neurofibromas), the assessment of unusual cases, and the application and assessment of new developments.

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## *Personal practice*

# Educating medical students about death and dying

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Doctors in every branch of medicine must from time to time deal with patients who are dying or who have life threatening illnesses. Many young doctors avoid facing their own feelings about death, finding them stressful.[1] When patients die we are perhaps reminded of the certainty of our own deaths.

In 1915 Freud[2] wrote: 'Our own death is indeed unimaginable . . . at bottom no-one believes in his own death, or to put the same thing in another way, in the unconscious everyone of us is convinced of his own immortality'. An inability to acknowledge death in a personal sense may account in part for our difficulty in approaching the subject[3] and everybody has some degree of anxiety about death.[4] This comes in part from the irreversibility of death, and in part from the impossibility of that experience being conveyed to others.[5]

We live in a society that rejects death, and doctors may have a greater need than others to do so.[6] Some authors suggest that doctors may compensate for their unconscious personal fear of illness and death by using distancing tactics[7] and other mechanisms in attempts to protect themselves through a process of mastery by becoming doctors.[8]

In medical training it is necessary for medical students to develop technical skills necessary to deal efficiently with illness. During this period, however, and without appropriate training and acknowledgment of the feelings elicited by medical work, it is likely that responses harmful to both doctor and patients will develop. Werner and Korsch[9] describe this process and show how spending time with a supportive group can help medical students become aware of the ways in which their own reactions can interfere with the effective treatment of patients.

It has been shown, however, that first year medical students did not differ from non-medical students in their attitudes towards death before they had direct clinical experience with dying patients.[10] Later on in their clinical studies medical students became more preoccupied with thoughts about their own deaths and the possible physical pain of dying, as well as about the breaking up of relationships as a result of someone else's death.[11] Death and some of the processes of dying may contradict the doctor's concept of his professional purpose,[3] and the death of a patient may be viewed as professional failure and generate guilt.[12]

Though in the past doctors tended to avoid breaking bad news to patients and their families, nowadays it is generally accepted that truthful information should be shared with them.[13–16] When children are concerned doctors are particularly ill prepared. For example Stein *et al* found that families in which there was a child with a life threatening illness remembered vividly the manner in which the diagnosis was imparted, and only about half the parents interviewed were satisfied with the way they had been told (Stein A, Woolley H, Forrest G, Baum JD. Imparting the diagnosis of life threatening illness. Paper presented at British Paediatric Association, York 1988).

Although doctors cannot prepare themselves for all possible circumstances that might arise regarding death and dying, some sort of preparation is necessary before a consultation with the family of a dying patient. A review of the cumulative Index Medicus heading 'Death' from 1960 to 1971 showed not one article about the teaching of medical students about death and dying.[6] Barton was one of the first authors to report his experience of working with groups of students on this issue.[3] He met groups of six to 10 students for one to two hours, and tried to focus their attention on death and dying and to examine and rationalise their personal feelings and attitudes towards the psychological and sociocultural issues that are an integral part of the care of patients with life threatening illnesses. In 1973, Liston reported that since the late 1960s about half the medical schools in the United States had included some formal teaching on death and dying in the curriculum,[17] and by 1980, 104 out of 114 (92%) medical schools in the United States had courses about death and dying.[18] In England in 1983 only four of 62 medical schools reported the absence of a programme for medical students on death and dying,[19] but often these were only an hour in a five year course.

A consensus had therefore been reached that medical students required education about the way to approach the dying patient and his family, and instruction on coping with these difficult issues. There is, however, no general agreement about the timing or the form of this education. Here we report on two different courses run by the authors for medical students in their clinical years—one in their child psychiatry, and the other in their medical attachment.

## The child and death

At the Royal Free Hospital medical students have one seminar in their preclinical psychology course on the psychology of grief, which includes the processes of normal grief and pathological grief reactions. One of us (DB) introduced (in 1985) a seminar on death and dying in the child psychiatry teaching which takes place during the paediatric attachment. This arose because of a special interest she had in the effect of loss by death on children and families.[20 21] The hospital chaplain gives six hours teaching on the ethical aspects of death and dying to clinical students on their obstetric and gynaecology, and general practice attachments.[22]

The one and a half hour seminar in paediatrics and child psychiatry can therefore concentrate on children, giving the students an experience of breaking bad news to parents and child by playing the parts. It also covers the developmental aspects of grief and mourning in children and adolescents[23-25] and touches on the effects on a child when a parent dies.[26]

The students are given the hospital's guidance booklet for staff on the *Care of the dying patient.*[27] Using techniques adapted from the teaching of family therapy, the tutor gives most of the 12 students in the seminar group the opportunity to experience the difficulties and frustrations of the doctor, or the pain and anger of the parents, by playing the parts.

Although students are initially resistant to exposing themselves to their peers in simulated doctor parts, if each one has only a short turn and is replaced by another, the various ways of approaching the task can be explored and discussed. The agony for each student is short but it enables each one to have an experience that seems to be important, and it reduces defensiveness. The evaluation from the students is positive.

## Dying patients and their families

While she was a senior registrar at the Whittington Hospital, JN, together with a psychiatric registrar and social worker, organised seminars for first year clinical medical students from University College Hospital on how to talk with dying patients and their families. Their only formal teaching on this subject is two talks of one hour each during the introductory course and before their preclinical attachments.

We offered this because the one and a half hours allocated to the teaching of interviewing skills was not adequate to cover this topic, and because the students expressed concern at the lack of teaching about death and dying: their theoretical knowledge helped little when talking to 'real' patients, and they felt overwhelmed by their own feelings when trying to talk about dying with patients and their families. Our aim then was to help medical students develop skills for dealing with dying patients and their families.

After discussion between the Dean of the medical school and the consultant child psychiatrists, a group of 20 third year students was offered an optional extra three hour teaching session led by two teachers. Preparatory meetings usually resulted in personal and professional bereavements being discussed; it was thought that this was likely to happen with the students too, and extra time was allowed for this. Little theory was offered but a leaflet, reading list, and two articles were given out at the end.[10 28]

In the introduction, normal grieving was described and students asked to describe their own experiences since being on the ward. They talked readily about the discomfort and anxiety they felt, and drew up a list of distancing tactics,[7] together with their thoughts about why they might be used. They were asked how they would like to talk to patients and their families. What factors would they want to take into account and what would they not want to do?

In the first section, the students played the part of a doctor telling a patient about her terminal illness. They were told 'she has six months to live' as, without that, discussion of the patient's imminent death could easily be avoided. The encounter was recorded on video tape and reviewed together after 10 minutes. Distancing tactics immediately became apparent and were discussed in the review. The students were often shocked by their emotional responses and were also able to get some idea of a patient's reaction to what they had said. Reviews of each session were necessary to avoid any student being left in the uncomfortable part of a dying patient.

The next section began with a talk on family reactions to loss and the mechanisms used to avoid facing the death—ones that doctors may easily and unwittingly use themselves.[29] A short 'play' in which everyone took part was performed, in which a family was visited in turn by a general practitioner, a vicar, a neighbour, and a relative after a sudden recent bereavement. The students were able to see how families rearrange themselves and roles change quickly to fill the gap left by the dead person.[30] Older children take on the part of a parent if an adult dies, and younger children are often ignored. Students found this approach powerful, and it often led to discussion of personal losses and unresolved grief. In the reviews of the sessions their own responses and personal experiences were shared, and the application of such sessions to their clinical work was discussed.

## Responses by students

Attendance at the seminars was voluntary; the group was therefore self selected and the number variable. Almost 100 students attended over two years, the ratio of women to men being 5:1. Those who attended and filled in evaluation forms found it helpful and requested more. Typical responses were: 'Though terrifying, the role-play helped me to see a bit of what it felt like to be a patient.' 'I never realised how little a patient could take in of what I was saying.' 'It will make it easier to talk to patients about what they are feeling.'

Such experiences are not yet recognised as being necessary in the training of medical students and the courses stopped when JN moved to another post. If formally integrated into the teaching, it would be possible to measure its effects accurately, and find out whether those medical students with more training in this area experience less stress when they become junior doctors.[1]

The value of a single teaching session is bound to be limited and it was frustrating for the teachers not to be able to see the students again. A regular series of meetings might have been more helpful so that individual patients could be discussed in detail and an attempt made to integrate the social, psychological, and medical aspects of death and dying.

## Discussion

In the early 1970s most of the courses on death and dying were given in the preclinical years,[12] and the preferred time to approach the subject was during courses in anatomy and pathology,[3] thus preparing students for the clinical years when they would meet patients with terminal illnesses. Linn *et al* suggested that because there was no difference in students' attitudes towards death and dying in preclinical and clinical years it would be more appropriate for these special subjects to be taught during the clinical years when the students actually experienced circumstances of death and dying.[4] As with the teaching of physical examination (which is done in small groups with self examination before the actual examination of patients) Liston recommended that students should not first learn about death and dying during bedside teaching.[6] Both formal lectures given by experts from different disciplines and small group discussions are needed for a comprehensive approach.[31]

From our experience in working with students on this subject we would like to recommend that each course should have the following objectives:

- To identify the dying patient's needs and wishes
- To understand the family's needs
- To recognise the phases of normal grief and mourning
- To be aware of cultural and religious aspects with regard to death and the roles of other people, such as chaplains, in caring for the person and the family
- To clear away the barriers that have been erected around the subject
- To make the student appreciate his or her own death, thus contributing to his or her emotional development
- To appreciate the need to relieve the physical and emotional distress of the dying patient[32 33]
- To consider ethical issues such as euthanasia, abortion, organ transplantation, and so on.

Different educational methods could be used in these courses, including formal lectures, discussions, interviews with patients, video tape illustrations of particular events, actors simulating patients and family members, students playing different parts,[34] and students being assigned to a dying patient and his family until the death and for some time during the period of bereavement.[35]

We suggest that the best time to offer such a course is in the clinical years when students have had some experience of clinical work. We recommend that no course be less than six hours and that teachers may come from any discipline but share an ability to communicate the skills of a clinician in reaching out to families in distress.

## Conclusion

There is no one way leading to death, and there is no one way of teaching students how to approach the issues of death and dying. The removal of the taboos about death, however, and the development of a structured comprehensive educational programme for medical students on terminal care, death, and dying in different stages of their studies, will improve the future physicians' skills in handling delicate and sensitive moments in their patients' lives.

There is still a danger that our medical training is teaching us that our tools are more important than we are.[36] By encouraging the acquisition of technical skills and factual knowledge but undervaluing our human reactions to the people we meet, medicine can become a dehumanising process[37] rather than one in which our human qualities can be used in conjunction with our technical knowledge to offer patients and their families a complete rather than a compartmentalised treatment.

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## *Medical education*

# Liaison psychiatry in a child development clinic

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### The problem

Children with mental handicap and other developmental disorders are normally cared for by their families. This represents an important shift from the previous practice when psychiatrists in large hospitals for the mentally handicapped provided total care and organised medical support. The medical and educational needs of such children are now met by resources in the community. This has often meant that the psychiatric needs of mentally handicapped children and their families were ignored. In 1968 the Sheldon Working Party recommended that district handicap teams and child development clinics should provide a comprehensive diagnostic and therapeutic service for mentally handicapped children. The Court Report stated explicitly that psychiatric consultation should be readily available to children and families seen by such services.[1] Some new job descriptions require child and adolescent psychiatrists to accept this responsibility, yet many of them feel inexperienced in this area of clinical practice.

It has been recommended that child and adolescent psychiatrists in training 'must have the opportunity to participate in the work of a service to psychiatrically disturbed mentally handicapped children'.[2] In practice, arranging suitable experience has proved difficult. Although most children with mental handicaps and complex developmental disorders are known to their local child development clinic or district handicap team, and are the patients of the local developmental or community paediatrician, there is not often much liaison between developmental paediatricians and child psychiatrists. A senior registrar post in child and adolescent psychiatry was therefore established at St George's Hospital with special responsibility for children and adolescents with complex developmental delays and mental handicap (figure).

### NATURE OF THE POST

The senior registrar works for two consultants—a child psychiatrist and a consultant in the psychiatry of mental handicap—both of whom have a special interest in children with complex developmental disorders. This 15 months' job is part of the four year higher specialist training in child psychiatry at St George's Hospital. Supervision takes place at weekly meetings with each of the two responsible consultants (PDH and SCH) alternately, as well as during shared cases and consultations with them or the consultant paediatrician (DMH). The key component of the post is to liaise between the child and adolescent psychiatry department and the child development clinic at St George's. The latter is a well established multidisciplinary clinic staffed by a developmental paediatrician, a speech therapist, a social worker, an occupational therapist, and physiotherapists, who provide both a local service and a centre of expertise for referrals from a distance, usually for second opinions. Before the post was created there was already a good working relationship between the personnel in the child development clinic, the child and adolescent psychiatry services, and the department of mental handicap, with some consultations being offered and occasional referrals exchanged. There was, however, an overall feeling that they were three distinct departments, and the first holder of the post was asked to develop the liaison aspect of the service. He was able to become an active member of the child development clinic, attended regular staff meetings, offered staff support, saw patients with their therapists, and took on specific referrals for assessment or treatment.

The senior registrar became a member of a child liaison group, a multidisciplinary group from the mental handicap services that offered consultation and some direct intervention for mentally handicapped children. By his working in paediatric, child psychiatric, and mental handicap services, communication was made easier and inevitable misunderstandings were minimised. This is particularly important when a number of professionals work for

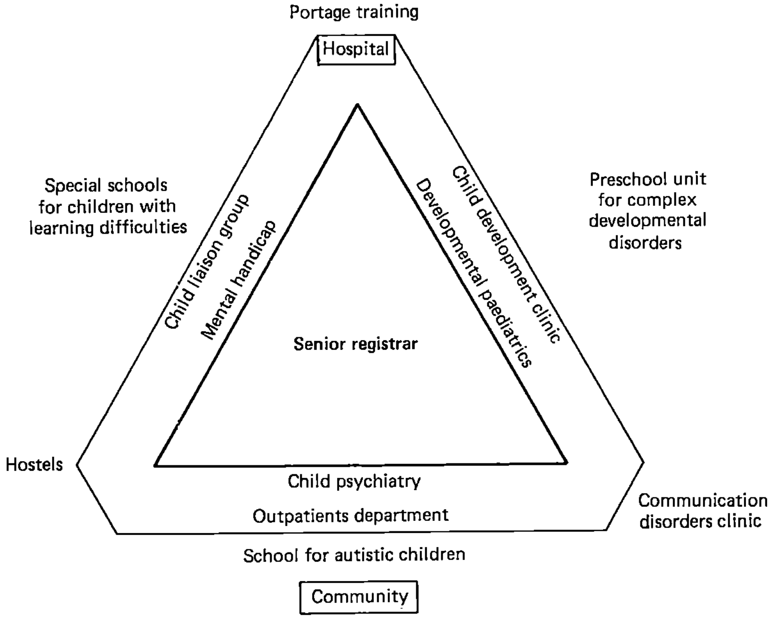
Portage training
Hospital
Special schools for children with learning difficulties
Child liaison group
Mental handicap
Child development clinic
Developmental paediatrics
Preschool unit for complex developmental disorders
Senior registrar
Hostels
Child psychiatry
Outpatients department
Communication disorders clinic
School for autistic children
Community

Figure *The senior registrar's position in the services for childhood developmental disorders.*

a long time with patients who are seriously developmentally disabled.

At the same time community links were established by the senior registrar providing regular consultation to local schools for children with severe learning difficulties, to a school for autistic children, and to a local day unit for preschool children with complex multiple developmental disorders. He joined the local Portage group* as a Portage visitor, helped supervise a support group, and subsequently ran training courses. Consultation was offered to social workers and staff in respite care hostels for children with mental handicap. All of this represented about half the week's work, the rest being spent in the department of child and adolescent psychiatry with both general referrals and those with developmental difficulties, together with general paediatric liaison, and personal training and research.

In the developmental disabilities component of the job the senior registrar was directly concerned with 53 cases as outlined below. He was also present in about twice that number of case discussions or combined interviews with the child development clinic staff, child liaison group, school consultations, Portage meetings, and consultations with social workers. It is not possible to subdivide these figures further because the patients were usually being helped by a number of agencies. The success of the service depended on the senior registrar coordinating treatment or aiding communication between different hospital and community workers.

This paper focuses on the liaison with the child development clinic, illustrating the contribution of the psychiatrist in three principal ways.

1 The integration of a psychiatrist into general paediatric work depends on active participation particularly by making referrals easier, and by paying attention to staff support.
2 The psychiatrist's participation in assessing developmental disorder is valued because of his knowledge of the interaction of biological, psychological, and social influences on maturation. These are adjuncts to his colleagues' sophisticated understanding of neurological, motor and linguistic development.
3 The psychiatrist's therapeutic skills are versatile in that they can be used with children with developmental disorders and shared with other professionals.

## Role of the psychiatrist in the child development clinic

### MAKING REFERRAL EASIER

It is a well established principle of liaison psychiatry that the immediate availability of a psychiatrist makes referral easier.[4] Sensitivity to the appropriateness of a psychiatric referral is likely to be particularly pronounced in a child development clinic. Firstly, there is a particular concern that parents will misunderstand a paediatrician's request for psychiatric help as another indication of their failure.

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*Portage: the Portage home visiting service for parents of children under 5 years with special needs to encourage home based teaching of appropriate developmental skills.[3]

Secondly, the long term relationship between the family and the clinic staff means that the referral cannot be handed over, but the psychiatrist must join in the work of the clinic and be seen to offer a continuity of care.

The senior registrar made himself easily available, attending clinic meetings, offered consultation to the relevant staff, or joined in interviews with the professionals and the family. Further clinical action hinged on the outcome of such meetings. One obvious consequence of this active liaison was a dramatic increase in the number of referrals for psychiatric assessment or treatment. Another was the development of a more positive view of psychiatric help, as was documented by a small independent survey of attitudes among the clinic staff.

### ASSESSMENT

Bax suggested that developmental paediatrics and child psychiatry have large areas of theoretical interest in common, but often there is a failure to communicate about them.[5] Our experience was that the psychiatrist was able to contribute to the assessment of the relative contribution of the biological, social, and psychological factors that are associated with developmental delay. An understanding of how individual and environmental influences interact helped to diminish any tendency of the clinic staff to assign the developmental delay to a single cause. Sometimes it was necessary to emphasise the effects of individual characteristics of children on their development. For example, a 3 year old with cerebral palsy showed severe separation anxiety with tantrums. The effects of the child's delayed motor development on the attachment process and an explanation of the concept helped to explain the behaviour, reduce parental tension, and establish a programme to encourage a gradual separation in a sensitive way. In addition the importance of adverse family or social factors needed assessing—as in the case of another child with cerebral palsy who was behaving oddly and whose mother had a manic depressive illness. Thirdly, knowlege of the possible mechanisms that underlie the association between developmental delay and psychiatric disorder was important. The disruptive behaviour of a child with severe language delay could be understood both in terms of the child's frustration and in the ways in which he was particularly unrewarding for his adoptive parents.

The reactions of families to the birth and development of handicapped children have been well described.[6] Understanding normal and abnormal reactions to the diagnosis was helpful, as in the case of a family who appeared unable to manage minor behavioural difficulties in their 5 year old who had severe learning difficulties. It was discovered that the family knew of a child who had had a successful operation for hydrocephalus and, while still in a stage of prolonged 'grief', they felt unable to deal with their child until he was likewise 'cured'. Acknowledgment of their difficulties freed the family so that they could take a positive approach and deal rapidly with the behaviour problems.

The child, family, and society may have inappropriate attitudes to disability that result in greater impairment. Appreciation of this was useful in the case of an 8 year old mentally handicapped girl who had recently arrived from Pakistan and was unmanageable at home. The senior registrar recognised that the family, privately, saw her as 'mad' and thought that she should be restrained. Discussion about the nature of her learning difficulties made for a more positive relationship with her parents, who then found her appropriate household tasks and valued her academic achievements.

As well as making these contributions, the psychiatrist learnt a great deal about assessment of neurological, motor, and linguistic disability. A 'communication disorders' clinic facilitated multidisciplinary assessment of children with complex language, social, intellectual, physical, and emotional disorders. Here the psychiatrist joined the paediatrician, clinical psychologist, and speech therapist in assessing the relative importance of a variety of developmental factors.

### TREATMENT PROVISIONS

Skills normally deemed the province of psychiatry, though obviously not confined to it, were gradually established as areas of competence within which the senior registrar could contribute effectively.

(a) *Consultation* was offered to clinic staff about the management of problems that previously would have been thought insufficiently serious by them to warrant a formal referral. For example, a therapist was concerned about the parents of a boy with severe language impairment who were unresponsive to his progress. The senior registrar suggested that the parents and the therapist should view the child through a one way screen to explore the parents' unhappiness and to work out how to encourage the child. As a result the parents were less critical and the pace of his speech therapy accelerated.

(b) *Counselling* of parents who were distressed or exhibited morbid attitudes to their child's disabilities is usually dealt with by medical social workers. The senior registrar offered alternative strategies or short term intensive treatment, as required. In one case a social worker had been giving long term support to a mother with an ambivalent attitude to her 6 year old boy and to the cause of his developmental delay. The senior registrar was asked to help with the boy's overactivity and enuresis, although it was felt that mother would be unable to cope with the necessary tasks. While carrying out a number of practical behavioural interventions, the senior registrar was able to explore the mother's guilt and anger, aspects of which she had previously been unable to discuss. This diminished her need to look for a new explanation for her child's problems as well as being able to develop a kinder but firmer style of parenting.

(c) *Formal family treatment* was sometimes indicated, for example, in exploring marital and sibling tensions about the effects of dealing with the special needs of a developmentally delayed family member.

(d) *Group treatment* is particularly appropriate in an area where sharing distress and coping strategies is especially helpful. A group was led by the senior registrar and a clinic social worker for parents of newly diagnosed mentally handicapped children where grief, anger, fears for the future, and practical information were shared.

(e) *Individual psychotherapy* was used for some children and parents—for example, a quiet and compliant child with a severe expressive language disorder used individual sessions with the psychiatrist to play out his frustrations about not being able to communicate.

(f) *Advice about psychotropic drug treatment* was sought, though this was not commonly implemented. Low dose neuroleptics such as haloperidol were usually only recommended in conjunction with behavioural treatment. The use of benzodiazepines was discouraged in view of their frequently disruptive effects on behaviour. A few children were given methylphenidate after assessment. Experience of the uses and psychological side effects of anticonvulsants were shared.

(g) *Child care legislation and court work*—from time to time cases were seen in the child development clinic that were the subject of legal proceedings. The senior registrar was a key figure in the assessment of parenting skills of a moderately mentally handicapped woman. A second case hinged on whether a mentally handicapped child might remain with his mother who had attempted a mercy killing shortly after hearing the diagnosis.

### STAFF SUPPORT AND TRAINING

Perhaps the least obvious but most crucial indication of the success of the integration of the senior registrar into the clinic was the development of staff support. Professionals dealing with children's chronic developmental problems have long term relationships with patients and families that can be highly distressing. The staff in the child development clinic shared in the families' grief for the loss of a 'perfect' child after diagnosis, and in the awareness of the child's limitations. In some difficult cases therapists knowingly concentrated on individual work with children, thereby avoiding exposing themselves to the parents' distress. Increasingly, professionals turned to the senior registrar for verification or guidance about their response to psychological problems in the child or family.

The senior registrar was asked to teach a wide range of professional groups concerned with paediatrics, child psychiatry, and the adult mental handicap service. This included running a Portage course, teaching Portage visitors, and teaching staff from the child development clinic and the local nursery to help parents foster their children's developmental skills. Supervision was given to the local Portage service in behavioural techniques and coping with family distress. By visiting a family the skills of ongoing structured teaching were gained.

## Conclusion

It is important to stress the two aspects of the liaison experience that have made this job a success. Firstly, the senior registrar was able to learn from the developmental approaches of the physiotherapists, occupational therapists, speech therapists, and paediatricians. There was a clear understanding that each discipline had skills to teach as well as to learn. Secondly, the senior registrar proved his worth by exercising his skills and by linking the three hospital services (paediatrics, child psychiatry, and mental handicap) with schools and nurseries in the community. The success of a community programme depends on the links between medical services, social services, and educational facilities. This complex multidisciplinary service and the chronic nature of the patients' developmental problems means that communication between institutions is vital. The senior registrar helped to provide these links by visiting community facilities as well as by being part of the three services in the hospital.

The overlap in clinical skills among the various disciplines in child development services is well recognised. It is therefore worth considering whether this valuable training for a child psychiatrist is specifically the province of psychiatry. The discussion shows that many cases could be seen by other professionals, such as clinical psychologists or social workers. All such disciplines offered a service to the clinic at the time in question. Of the 53 referrals from child development clinics and related services, a quarter required a psychiatrist's special skills. These included, firstly, the assessment or treatment of parents and children with severe mental illness (including prescribing antidepressant drugs for a mother after the diagnosis of her child's disabilities, and neuroleptics for a schizophrenic adolescent). Secondly, medical training was essential in understanding the problems of children with severe organic disease—for example, a child with Rett's syndrome. Thirdly, appearing in court as an expert witness is particularly a medical responsibility. Fourthly, medical and psychiatric training provide the important theoretical knowledge that is necessary to make an adequate assessment of causative factors in complex developmental problems. Fifthly, in some circumstances a formal medical consultation is the usual approach, and is best received by concerned professionals—for example, when a psychiatrist works with a medical officer in schools for children with special learning difficulties.

For the senior registrar himself the opportunities provided by working with families and professionals in a child development clinic are an ideal way of fulfilling the relevant requirements of the Royal College of Psychiatrists, as they apply to higher training in child and adolescent psychiatry. Paediatrics and child psychiatry overlap in a number of areas of clinical practice; this seems to be one area where they should also overlap in training.

We thank the staff of the Child Development Clinic and the many professional people in the community who encouraged the setting up of this liaison.

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# Correspondence

## Glucose intolerance in cystic fibrosis

Sir,

Stutchfield *et al* in their studies of glucose intolerance in children with cystic fibrosis report pancreatic islet cell antibodies in five of 24 patients with glucose intolerance identified by raised glycated haemoglobin ($HbA_1$).[1] They suggest that an autoimmune response to damaged pancreatic tissue may promote the development of glucose intolerance. We would like to suggest a further factor that appears to influence glucose tolerance and may be relevant to the interpretation of glucose tolerance tests and the subsequent development of insulin dependent diabetes in cystic fibrosis.

We have recently reported a modified Ussing chamber technique to study ion transport in the cystic fibrosis enterocyte using jejunal biopsy tissue.[2] The basal potential difference, short circuit current, and resistance of 22 control biopsy specimens and 11 biopsy specimens from patients with cystic fibrosis are shown in fig 1. Initial differences in potential difference and short circuit current probably reflect basal secretion in the control tissues, which is absent in epithelia in cystic fibrosis. Both chloride secretion and nutrient absorption are active electrogenic processes whose activation can be detected as a rise in short circuit current. All control biopsy specimens responded to the stimulation of chloride secretion by acetylcholine with an increase in short circuit current but the specimens from patients with cystic fibrosis failed to exhibit such a response (fig 2). This indicates the lack of a functioning chloride secretory mechanism similar to that observed in other affected epithelia.[3] Both control biopsy specimens and those from patients with cystic fibrosis generated an increase in short circuit current when glucose was added to the luminal surface but this effect was significantly greater in the specimens from patients with cystic fibrosis. This suggests that glucose uptake is enhanced in cystic fibrosis, an observation that has also been noted in in vivo perfusion studies.[4] The relative glucose intolerance seen in cystic fibrosis may therefore be a consequence of an increased rate of glucose absorption.

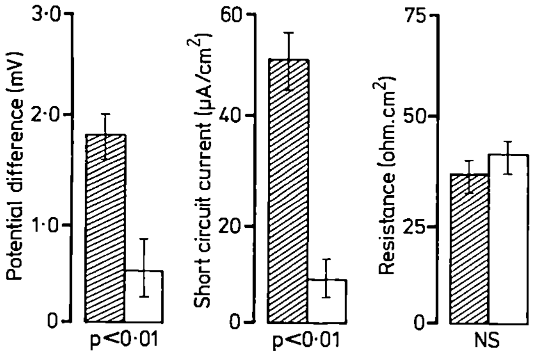

Fig 1 *Bar diagram showing mean (SE) basal electrical activities of jejunal tissue from controls (hatched) and patients with cystic fibrosis (clear).*

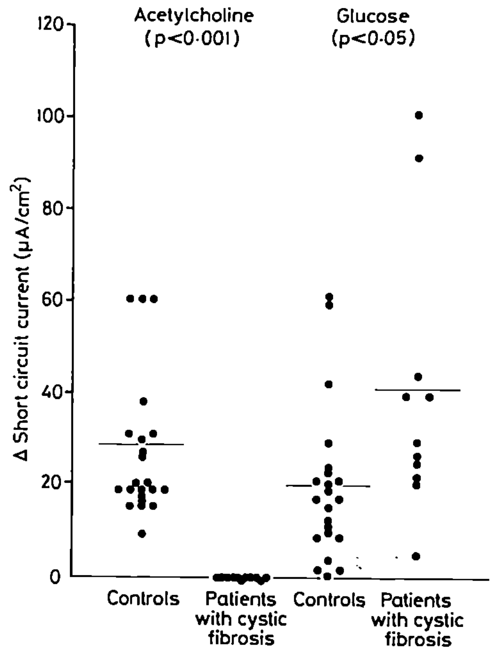

Fig 2 *Response (Δ short circuit current) to secretagogue challenge (acetylcholine, $10^{-3}M$) and mucosal glucose ($10^{-2}M$) in biopsy specimens from controls and patients with cystic fibrosis.*

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## $^{99m}$Tc dimercaptosuccinic acid (DMSA) scan in urinary tract infection

Sir,

Dr Smellie *et al*, in their recent paper on $^{99m}$Tc dimercaptosuccinic (DMSA) scan in patients with established renal scarring,[1] quoted a paper from this hospital.[2] They failed to quote the principal findings of this paper, however, namely that a DMSA scan is the most accurate method of detecting renal scars in children 0–5 years old. In our paper we compared intravenous urograms, ultrasound, and a DMSA scan carried out over a six month period in 63 children known to have vesicoureteric reflux. A total of 60 children were found to have scarring on DMSA scans, 50 on ultrasound, and only 36 on intravenous urograms. The severity of the scarring was assessed and a highly significant difference was obtained for coupled comparisons of the three modalities—that is, between DMSA scanning and ultrasound, ultrasound and intravenous urography, and DMSA scanning and intravenous urography. None of the changes identified on a DMSA scan in this group was reversible indicating that the appearances were not the result of recent acute infection.

The data were also assessed according to the age of the children, and the discriminating power between the techniques became less noticeable with increasing age.

In our hands $^{99m}$Tc DMSA scanning is neither expensive nor time consuming (about £35 per examination). Reactions to DMSA are exceptional but there is still a definite morbidity and mortality associated with contrast media, even the non-ionic form. In our department scanning is carried out 1·5 hours after injection and takes 15–20 minutes. We never perform DMSA and diethylenetriamine pentacetic acid (DTPA) scans simultaneously.

In this hospital the DMSA scan is used as the first line investigation of the renal tract in urinary tract infection. Intravenous urography is carried out only for assessment of possible structural abnormality, particularly before surgery. Reliance on intravenous urography and ultrasound, especially in those under 5 years old, will result in inadequate detection, treatment, and follow up of renal scarring.

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## The teenage coeliac: follow up study of 102 patients

Sir,

We read with interest and pleasure the paper by Kumar and colleagues on the teenage coeliac.[1] We were surprised, however, that height distribution of their teenagers with coeliac disease was nearly normal despite the fact that nearly half of them (45/102) confessed not to adhere to the gluten free diet and most (36/44) of the biopsy specimens showed jejunal mucosa abnormality.

In our longitudinal study we followed up 43 children with coeliac disease who, after initial diagnosis at the mean age of 13 months (range 4–31 months) and a gluten free diet for one to three years (mean 15 months), abandoned this treatment and returned to a normal gluten containing diet.[2] We followed patients up with a yearly clinical and anthropometric assessment and a duodenal biopsy. There was a gradual decrease in the number of the assessed patients because they either returned to the gluten free diet or were lost to follow up. All measurements were interpolated by Tanner's method to obtain data at regular yearly intervals. Such interpolated data were transformed into standard deviation scores (SDS) according to Tanner's formula SDS=(xe–Xm)/SDm where xe is the measurement at the relevant age and Xm and SDm are normal mean and normal standard deviation at the age in question, respectively (see table). Means of standard deviation scores were compared with the normal means by the Student's *t* test for unpaired groups. We found that at each of the yearly age intervals the persistent histological relapse was paralleled with significant height deficit.

Similar linear growth retardation was evidenced by Colaco *et al* in their cross sectional study of Irish adolescents with coeliac disease aged between 17·8 and 18·5 years—therefore after their pubertal spurt.[3]

The 102 coeliac children reported by Kumar *et al* are a 'mixed society'; more than half (58/102) did not have a biopsy specimen taken at the time of the study. Of the 44 who did have a biopsy, eight had normal mucosa, 19 showed moderate and 17 gross abnormality. Some of these children were at their pubertal spurt, some were older. It is

Table *Mean and SD of height expressed as standard scores (SDS) at yearly age intervals in children with 'neglected' coeliac disease and persistent histological relapse*

| *Age at assessment (years)* | *Mean height SDS (SD)* | *p Value* | *No of patients* |
|---|---|---|---|
| 3 | −0·65 (0·88) | <0·001 | 35 |
| 4 | −1·10 (0·90) | <0·001 | 29 |
| 5 | −0·76 (0·90) | <0·001 | 24 |
| 6 | −1·08 (0·84) | <0·001 | 19 |
| 7 | −0·86 (0·97) | <0·01 | 16 |
| 8 | −1·06 (0·81) | <0·001 | 15 |
| 9 | −0·85 (0·67) | <0·01 | 10 |

a fact that the pubertal spurt may improve not only auxology but also the underlying jejunal pathology. Therefore it is very difficult to analyse auxology of children in such a period. The number of the investigated patients is so impressive that it would be possible to analyse separately those patients who had adhered to a gluten free diet and those who had not complied with this regime.

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## Leukoencephalopathy after prophylactic radiation for leukaemia in ataxia telangiectasia

Sir,

In their short report, Eyre and her colleagues remind readers of the possible harmful effects of therapeutic doses of radiation treatment and tumour chemotherapy in patients with ataxia telangiectasia.[1] Although the radiological appearances in their patients seem consistent with a diagnosis of treatment induced encephalopathy, is it certain that these findings were not those of ataxia telangiectasia itself? What are the findings on computed tomography in children over 5 years with 'uncomplicated' ataxia telangiectasia.

Assuming that this objection can be countered, I wish to challenge the contention, at the end of the report, that '. . . in children with acute lymphoblastic leukaemia prophylactic cranial irradiation and intrathecal methotrexate should be either withheld or given in reduced dosages'. This recommendation, as far as radiation treatment is concerned, is correct but for methotrexate is misleading and potentially mischievous, for the following reasons: Eyre *et al* claim that 'histological examination showed features diagnostic of a *chemoradiation induced* leukoencephalopathy' (my italics); however, so far as I am aware, there is no evidence in the literature that radiation treatment induced and radiation treatment/chemotherapy induced damage in ataxia telangiectasia are histologically distinguishable. Radiation treatment is an acknowledged cause of cellular damage in ataxia telangiectasia, both 'in vitro' and 'in vivo',[2] whereas only a few drugs in clinical use—for example, bleomycin[3]—have been implicated. 'In vitro' data for other drugs is not readily available but children with ataxia telangiectasia have been reported to tolerate systemic methotrexate/6-mercaptopurine treatment in normal doses.[4] It would be interesting, in the Newcastle case, to know the temporal distribution of the reported 'gaps and reductions' in methotrexate/6-mercaptopurine treatment. If most occurred during the first year of treatment, rather than the second, it may be that lingering radiation treatment induced DNA damage to bone marrow in the craniocervical area, rather than chemotherapy, was blameworthy. A possible increase of vinca-alkaloid induced neurotoxicity has been noted in one report, but is not mentioned in others.[4] This report, which includes a literature review, also contains the specific statement 'No adverse effects from monthly intra-thecal methotrexate were noted in our patients'.

Although ataxia telangiectasia is itself very rare it is relatively more common in the selected group of children who develop acute lymphoblastic leukaemia or malignant lymphoma. While it is clear that radiation treatment must be given in reduced dosage—if at all—to patients with ataxia telangiectasia,[2] and though vincristine is still 'sub judice' it would be unfortunate if intrathecal or systemic methotrexate (or systemic 6-mercaptopurine, asparaginase, or anthracycline) doses were automatically scaled down or omitted. For children with ataxia telangiectasia and acute lymphoblastic leukaemia or lymphoma, the likely outcome would be an increased relapse rate. In many countries children's cancer treatment is now coordinated by national children's cancer study groups. Specific treatment recommendations for children with ataxia telangiectasia and malignancy are needed and could be publicised by these groups (in this country, the UKCCSG).

Incidentally, the terms 'central nervous system prophylaxis' and 'maintenance treatment', as used in the article, are inaccurate and archaic and should be abandoned.[5] 'Central nervous system-directed treatment' and 'continuing treatment' are preferred alternatives.

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Drs Eyre, Gardner-Medwin, and Summerfield comment:

Dr Pritchard's points are important ones and we very much agree with his main premise that no form of chemotherapy that might be life saving should be discarded without sufficient evidence of its neurotoxicity in children with ataxia telangiectasia. We would like, however, to make the following comments in reply.

First, the appearances found on the computed tomogram in our patient are not seen in uncomplicated ataxia telangiectasia and resemble more closely those seen in methotrexate induced encephalopathy[1] rather than in radiation encephalopathy.

Second, the neuropathological changes found in the brain biopsy were 'a variable degree of demyelination accompanied by a florid astrocytic reaction and spongiform change. Small fragments show total necrosis in the absence of a cellular reaction and there is considerable fibrin deposition accompanied by haemorrhage suggesting a subacute vasculopathy of some months standing'. The vasculopathy might well be a feature of radiation encephalopathy but the overall findings are more consistent with those found in methotrexate induced encephalopathy.[2]

As we said in our paper we also regarded the experience of Toledano and Lange[3] as evidence that in ataxia telangiectasia intrathecal methotrexate treatment without cranial irradiation could be followed by neurological deterioration (case 5 in their review). The case report by Abadir and Hakami also suggests that there may be increased sensitivity to methotrexate in ataxia telangiectasia,[4] and in fact Dr Pritchard and his colleagues acknowledged in the discussion following their reported case that there was evidence in the literature of an increased neurotoxicity from intrathecal methotrexate in ataxia telangiectasia.[5]

Dr Pritchard requests further details about the gaps in chemotherapy. In the first year treatment was withheld for 14 weeks and in the second for five weeks. The doses of chemotherapy, however, were decreased in the second year to allow more continuous treatment and thus in the first year the total dose of mercaptopurine was 8680 mg and of methrexate was 365 mg and in the second year the total doses were 8540 mg and 395 mg respectively. It is unlikely that radiation induced damage to the negligible amount of bone marrow in the craniocervical area was the cause of our patient's intolerance to chemotherapy.

It is clearly very important that any available experience with chemotherapy in children with ataxia telangiectasia should be carefully recorded in the literature as soon as possible. I am sure we all agree that specific recommendations for the treatment of children with ataxia telangiectasia and a malignancy are needed urgently. These perhaps would be best devised and publicised by the UKCCSG. Finally we would like to reiterate our main point that preexisting motor handicap, even if it is mild and apparently non-progressive, in a child with a malignancy should ring alarm bells about possible ataxia telangiectasia.

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## Outcome after antenatal diagnosis of upper urinary tract dilatation by ultrasonography

Sir,

We read with interest the paper by Gunn *et al.*[1] Although they reported a higher incidence of antenatally detected urological abnormalities than in most other published series, their experience in New Zealand is very similar to ours in a district general hospital serving a stable, well defined population in the north of England.

If their results are related to total births, rather than to the number of fetuses examined after 28 weeks' gestation, the incidence of abnormalities was 7/3228, or 2·2/1000 births, 1·6/1000 being pelviureteric junction obstruction.

During the period 1985–7, out of a total of 5762 births, we have found 13 cases of definite urological abnormality, a rate of 2·3/1000. Ten of these (1·7/1000 births) had pelviureteric junction obstruction, two hydronephrosis with megaureter, and one isolated megaureter. All 13 had intravenous urography and were then referred to paediatric surgeons who arranged isotope renography or micturating cystourethrography, or both, when necessary to establish a precise diagnosis.

These results are quite different from those reported recently by Scott and Renwick over the period 1984–6 from the Northern Region Fetal Abnormality Survey,[2] in which we participate. They found only 162 abnormalities in 121 849 births, a rate of 1·3/1000, and of those only 37 (0·3/1000) were 'hydronephrosis' (which we equate with pelviureteric junction obstruction). We have therefore detected many more cases of pelviureteric junction obstruction than this region as a whole, though a similar rate of other urological abnormalities.

Like Gunn *et al* we also found that, where recorded, the maximum dimension of the fetal renal collecting system was 15 mm or greater in all cases that proved to have definite pathology (table).

Table *Relation of fetal renal pelvic size to outcome*

| *Outcome* | *Maximum recorded dimension of fetal renal pelvis* | | | |
|---|---|---|---|---|
| | *<15 mm* | *15–25 mm* | *>25 mm* | *Not recorded* |
| Definite pathology | 0 | 5 | 9 | 1 |
| Minor variation from normal | 4 | 12 | 1 | 3 |
| Normal | 7 | 7 | 2 | 4 |

In some cases each kidney appears separately, therefore the total number is slightly higher than the number of cases.

We do not know what proportion of our patients were scanned in the third trimester, but during 1985–7 the mean number of ultrasound examinations per booked pregnancy was 2·7. In contrast to Gunn *et al*, six out of 15 cases of definite pathology detected to date were first suspected between 15 and 19 weeks' gestation. We agree with them, however, that in addition to a routine scan at about 18 weeks, every fetus should ideally have a further ultrasound examination after 28 weeks' gestation.

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## Mother's choice to provide breast milk and developmental outcome

Sir,

The recent paper by Morley *et al* discussed some of the dangers of interpreting the higher Bayley scores at 18 months that were achieved by very low birthweight babies whose mothers expressed an intention to breast feed compared with those whose mothers did not.[1]

In a detailed analysis of breast feeding and child development in the 1970 National Cohort (CHES), adjusting for all factors predictive of initially deciding to breast feed, strong relationships were found linking breast feeding decision to above average scores in a picture vocabulary test and a human figure drawing test at 5 years of age, and the Edinburgh Reading Test at 10 in both primiparae and multiparae. Furthermore higher average British Ability Scale scores characterised 10 year old children who were breast fed as infants.[2]

Language development and vocabulary and drawing skills at 5 years have now been examined for infants with birth weights of less than or more than 2537 g whose mothers breast fed their infant wholly or partially during the first seven days postpartum. In a multiple logistic regression analysis on both birthweight groups, the odds ratio of above average skills in the initially breast fed group were computed, having adjusted for the same factors predictive of breast feeding used by Morley *et al*: educational qualification of mother, mother's age and parity, marital status, social class, method of delivery, gestational age, birth weight, and sex of infant. No adjustment could be made for the number of days of ventilation as these data were not available. The results (table) indicate similar modest associations between initial breast feeding and intellectual outcome for both birthweight groups with small sizes and large standard errors probably responsible for the lack of significance in the low birthweight group.

Table *Adjusted odds of higher than average scores on three developmental tests at 5 years of age of children initially breast fed during the first week of life (1970 National Cohort)*

| | *Birth weight (g)* | |
|---|---|---|
| | *<2537* | *≥2537* |
| **Copying Designs Test** | | |
| Adjusted odds ratio | 1·09 | 1·13 |
| 95% Confidence intervals | 0·89 to 1·34 | 1·08 to 1·18 |
| p Value | 0·41 | <0·0001 |
| Sample size | 441 | 8146 |
| **Human Figure Drawing Test** | | |
| Adjusted odds ratio | 1·09 | 1·08 |
| 95% Confidence intervals | 0·88 to 1·35 | 1·03 to 1·13 |
| p Value | 0·42 | 0·0012 |
| Sample size | 430 | 8011 |
| **English Picture Vocabulary Test** | | |
| Adjusted odds ratio | 1·06 | 1·11 |
| 95% Confidence intervals | 0·86 to 1·32 | 1·06 to 1·17 |
| p Value | 0·57 | <0·0001 |
| Sample size | 416 | 7712 |

These results might seem to indicate support for a breast feeding effect. However, in further CHES studies of antenatal class attendance, smoking behaviour, and immunisation, similar associations with educational and intellectual outcomes can be linked to 'positive' health behaviour in the mother.[3] Caution is therefore demanded in interpreting the present results.

As Morley *et al* recognise, mothers of preterm babies prepared to breast feed are likely to comprise an especially motivated group. Their family characteristics are likely to be associated with above average educational stimulation of their children. Furthermore, one should be wary of linking 'intentions to breast feed' with substantial breast milk consumption as these may not be matched by 'actual breast feeding'. In the CHES study there was a high preponderance of very short term breast feeders.[4]

Conversely, intentions to engage in healthy behaviour are probably indicative of a wide range of motivations likely to be associated with advantageous parenting styles and favourable outcomes in the child. Only when breast feeding in the population is unrelated to socioeconomic advantage, mother's background, attitudes or personality, or other forms of health behaviour, can its long term impact on development and intellect be properly determined.

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## Brittle or battered?

Sir,

My attention has been drawn to correspondence about this subject. There is reference to an article in which I reported study of a series of children with osteogenesis imperfecta with special reference to the occurrence of metaphyseal fractures.[1]

In his letter Dr Blumenthal states that 'metaphyseal fractures are a feature of both abuse and brittle bones'.[2] This is true but needs qualification. In non-accidental injury the bones appear grossly normal and the metaphyseal fractures are often numerous. In osteogenesis imperfecta fractures of this type are infrequent and rarely number more than one or two. They were only seen in my series where there was *gross abnormality of the skeleton* and the diagnosis of the presence of a systemic bone disease was apparent at a glance.

To quote my last sentence, 'Confusion with non-accidental injury did not occur'.

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## Somatostatin analogue in short term management of hyperinsulinism

Sir,

We are interested by the report of Kirk *et al* of the use of somatostatin analogue for the short term management of hyperinsulinism in which a fall in glucose requirement of 4–6 mg/kg/minute was seen.[1] We have previously reported similar success, in the short term control of hyperinsulinism in an infant with nesidoblastosis, using growth hormone twice daily by subcutaneous injection.[2] A fall in glucose requirement of 5·5 mg/kg/minute was seen. The effect of growth hormone in the treatment of hypoglycaemia is reported elsewhere.[3] [4]

At the time of our report further studies of this use of growth hormone were precluded by the withdrawal of pituitary growth hormone after reports of Creutzfeldt-Jakob disease. Now that a growth hormone produced by recombinant DNA technology is available, however, the choice of growth hormone over a somatostatin analogue has advantages.

Somatostatin has a very broad range of endocrine activity,[1] with unwanted effects upon other endocrine axes that do not appear to be produced by growth hormone. Furthermore, on simply practical grounds growth hormone, unlike somatostatin, is available in most regional centres.

In the infant with hyperinsulism, when it is necessary to temporise before surgery, we believe that growth hormone may be preferable, and its use certainly merits further study.

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## Disialotransferrin developmental deficiency syndrome and olivopontocerebellar atrophy

Sir,

I read with great interest the paper of Kristiansson *et al* about disialotransferrin developmental deficiency syndrome.[1] I would like to draw attention to the remarkable similarity between this syndrome and a condition recently reported in two siblings as olivopontocerebellar atrophy with neonatal onset.[2] Common features included failure to thrive, hypotonia, developmental delay, joint restrictions, pericardial effusions, mild non-progressive liver disease, retinal dystrophy, and cerebellar hypoplasia.

Moreover there was thyroxine binding globulin deficiency in the patients reported by Harding *et al*,[2] and although serum concentrations of thyroxine binding globulin were not reported in the paper of Kristiansson *et al* thyroxine binding globulin deficiency was a constant feature in our patients who presented with a closely related condition.[3] The only difference was the clinical course of the condition, which was fatal in both patients (at 7 and 23 months) of Harding *et al* whereas the patients of Kristiansson *et al* and those reported by us were all alive (age 3 to 21 years).

I therefore recommend a search for defects in glycoprotein metabolism (particularly in the processing and synthesis of the carbohydrate moiety) in patients with olivopontocerebellar atrophy. A valuable screening method for this purpose is the carbohydrate deficient transferrin test devised by Stibler *et al*.[4]

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# Clostridium difficile in an oncology unit

Sir,

Brunetto *et al* describe a cluster of patients with *Clostridium difficile* and conclude that an outbreak had occurred.[1] However, I wonder whether this might, at least in part, have been a pseudo-outbreak. A previous paper reported a cluster of cases, but serotyping of the isolates showed that four strains were circulating and other investigations showed the cause of the outbreak to have been a virus rather than *C difficile*.[2]

In the incident reported by Brunetto *et al* only two of 21 patients had severe symptoms and in only 18 of 31 (58%) episodes of *C difficile* associated with diarrhoea was toxin detected. Colonisation rates almost as high as 40% have been reported for *C difficile* in oncology units in the absence of overt problems,[3] hence positive cultures in the absence of detectable toxin is of questionable significance.

Although the epidemic curve in the current incident appears most impressive, could the rise in incidence merely represent an increased level of investigation for *C difficile* rather than a genuine increase in prevalence? Typing the isolates by one or more methods might have strengthened or refuted the interpretation the authors place on their data.

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# Dehydration fever in the neonate—a common phenomenon?

Sir,

Rises in temperature are seen occasionally on the third to fourth day of life in infants who are otherwise well, and overheating and sepsis as causes of fever must be excluded.[1] Dehydration is perhaps an infrequently recognised cause of fever in the newborn period.

## Case report

A boy was born at term after a normal pregnancy and labour weighing 4000 g. The initial examination at 36 hours of age showed a temperature of 37·7°C but he was normal otherwise. He was breast fed and remained well until the age of 3 days when he developed a tachycardia and irritability and was found to have a temperature of 38·1°C that rose rapidly to 39·2°C. Investigations showed a serum sodium concentration of 153 mmol/l and a metabolic acidosis; plasma glucose and creatinine, full blood count, a chest radiograph, and cranial ultrasound scan were normal. Urine and blood cultures were sterile. After resuscitation with plasma the temperature fell to 37·9°C. The infant fed ravenously from the bottle. At discharge the plasma sodium concentration and urine osmolality had returned to normal and his weight had risen from 3620 g to 3810 g (figure).

The clinical features and results of investigations supported dehydration and excluded sepsis and overheating as the cause of this infant's fever. The dehydration was due probably to an inadequate intake of milk. Dehydration fever is seen most commonly in large breast fed babies whose milk intake is poor or in infants exposed to high environmental temperatures, with rises in temperatures to between 37·8 and 40°C.[2] Infants appear unhappy and may lose approximately 10% of their birth weight. Diagnosis

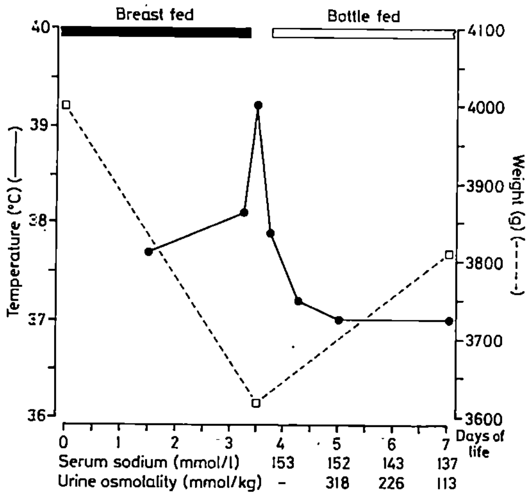

Figure *Time course of temperature, weight, serum sodium concentration, and urine osmolality in the infant.*

may be confirmed by measurement of urine osmolality.[3] Rehydration leads to lysis of the fever and resolution of symptoms. It is likely that dehydration fever occurs more commonly than is recognised; our patient almost certainly represents a 'severe' form of the phenomenon. In contrast with the detailed descriptions that were written over two decades ago, many of the current textbooks on neonatal intensive care make little or no reference to dehydration fever.

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*Archives of Disease in Childhood,* 1989, **64,** 767–768

# Book reviews

**Duchenne Muscular Dystrophy.** By A E H Emery. Revised edition. Pp 317: £17·50 paperback. Oxford Medical Publications, 1988. ISBN 0-19-261798-2.

These are exciting times for those involved with Duchenne muscular dystrophy. Now that the gene has been isolated and sequenced, and the protein 'dystrophin' which it encodes identified, we are at last established on the road to understanding the pathogenesis of the dystrophic process. Considering the tremendous interest in this disorder, there is clearly a need for a book that draws together all the various strands of current knowledge, and this is ably provided by Emery.

The author has covered every conceivably relevant aspect with chapters on the clinical features, methods of investigation, differential diagnosis, biochemistry, pathogenesis, genetics, molecular pathology, management, and more besides. It starts with a fascinating chapter on the history of the disease, from ancient Egypt to modern times, and ends aptly with Duchenne's obituary in the *Lancet.* The book contains many excellent illustrations. The text is commendably clear, particularly when explaining difficult concepts such as the use of DNA probes and the mathematics of risk calculation.

Inevitably one looks to see if the author has been able to keep the book up to date in this revised edition. He has included a section on dystrophin including important 1988 references. He has also discussed the various animal models, including the MDX mouse and the retriever dog, but was not able to indicate fully their relevance to the human condition. The only other omission is the theory of mechanical damage in the evolution of the dystrophic pathology, which is looking increasingly more relevant as time goes by. These comments notwithstanding, this excellent book is of potential value to any physician or basic scientist involved with this disease.

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**Prader-Willi Syndrome.** Edited by M Caldwell and R Taylor, Pp 110: hardback. Price not stated. Springer-Verlag, 1988. ISBN 3-540-96699-4.

The mere mention of Prader-Willi syndrome engenders in most doctors a blank look of incomprehension, but it is heartening that paediatricians are increasingly aware of the syndrome. This book presents 'selected research and management issues'; in fact it is mainly a review of the literature flavoured with personal experience of the two editors, both North American educationalists, and a psychologist, paediatrician, paediatric surgeon, and a geneticist.

The clinical features are first outlined, but is height really 'within normal limits during the first ten years of life'? Most surprisingly though, no mention of the characteristic facies is included although 'dysmorphic facial features' are referred to in a later useful chapter on aetiology. This deals mainly with the role of chromosome 15q12 stressing the importance of special chromosome preparations examined by experts accustomed to the syndrome. The hypothalmic disorder in the syndrome might usefully have been included here. 'Surgical Considerations' tackles problems that exercise both doctors and parents—well illustrated by an opening sentence '... non-surgical procedures usually succeed at least to a better level of satisfaction than surgery . . .'. Intestinal bypasses to prevent and cosmetic surgery to excise obesity both have complications which have to be balanced against possible benefit. Although poor testicular development at biopsy is quoted, orchidopexy is generally favoured, but I wonder whether this is justified? After all, testicular malignancy in association with the syndrome seems never to have been reported and cosmetic considerations seem to be more of an anxiety of parents than of patients. The necessary cooperation of the patient to benefit from surgery for scoliosis is discussed as are problems of intubation and hypothermia during anaesthesia, which sometimes complicate any operation in this syndrome.

Two chapters are about cognition and behaviour and its management but hypotheses outrun practical advice. Similarly, 'Management of Problems of Infancy' resolves into that of a hypotonic baby whatever the cause. Finally a chapter on 'Parent Concerns', based principally on an analysis of a questionnaire sent to only 12 families, emphasises the anxieties of parents and the need for all carers to communicate with them.

Most of all though, it is early diagnosis and a diagnostic 'label' that helps. The Prader-Willi Association in America is the most useful solace for parents, reflecting the experience of its counterpart in the United Kingdom. For those interested in the syndrome this is a useful book, but I could not give it a high priority on a medical library list.

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**Perinatal Events and Brain Damage in Surviving Children.** Edited by F Kubli, N Patel, W Schmidt, and O Linderkamp. Pp 338: DM 120 hardback. Springer-Verlag, 1988. ISBN 3-540-18111-3.

'The book of the conference' is often in danger of being a disappointment because it is usually published so long after the meeting that prospective readers feel it must surely be out of date, and the written word seems to lack the impact and immediacy of the spoken papers. In this case the editors have avoided these defects and achieved success with a book on a conference held in Heidelberg in 1986, organised by the committee on Perinatal Mortality and Morbidity of the International Society of Gynaecology and Obstetrics (FIGO). The conference was designed to explore the relationship between events in pregnancy and neurodevelopmental handicap in the offspring with the aim of 'separating scientifically based knowledge from myths'. The majority of the 62 contributors came from Europe and Scandinavia with a handful from North America and Uruguay. They covered the specialties of paediatrics, obstetrics, pathology, physiology, and epidemiology and the list of their names reads like an international Who's

Who in perinatology, consequently each of the papers has an air of authority about it.

The book itself is in seven sections each containing four to six papers, these have been written not as transcripts of the spoken word but as short chapters mainly in the form of a review of the current state of the topic with some also including the author's original data. The first section on the epidemiology of neurodevelopmental disorders is followed by sections on the pathogenesis of handicap, intrauterine growth retardation and chronic hypoxia, and acute intrapartum asphyxia and birth trauma. The conference then turned to the preterm and very low birthweight baby with papers on intraventricular haemorrhage and ischaemia, and reviews of the changing outcome for these infants showing improved survival and decreased morbidity. Finally, there are reports of four recent follow up studies from Dundee, Uruguay, Finland/Bavaria, and Hamburg.

I found this book to be much more than just the report of a conference, it contains a wealth of information of relevance to both paediatricians and obstetricians providing clear up to date views on an important area of perinatal care. The papers are well referenced but unfortunately there is no subject index, consequently there is no alternative but to read the book from cover to cover.

One of the contributors started his chapter with a quotation from Freud (1897) 'Difficult birth in itself in certain cases is merely a symptom of deeper effects that influenced the development of the fetus'. We are just beginning to appreciate how right Freud was, perhaps the lawyers ought to read this book as well, certainly all paediatricians should.

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**Manual of Hospital Paediatrics.** By Garry Hambleton. Pp 360: £14·95 paperback. Churchill Livingstone, 1988. ISBN 0–443–03512–1.

The Concise Oxford Dictionary defines 'manual' as a small book for handy use. As a description of the author's goal it would be difficult to better. Rest assured that Dr Hambleton achieves it, and in so doing invites favourable comparison with another English Midlands paediatric institution's handbook with a latin title.

The manual is well laid out, defining or describing each condition, listing causes, symptoms and signs, differential diagnosis, investigation, and treatment. Where relevant, simple practical advice o management and prognosis is offered giving clear guidance as to what to expec and, most importantly for a junior paediatrician, what to tell the parents. It scope ranges from the emergency situatio to the common or garden complaints tha all too often present in the small hours such as a blocked nose or a painful ear though sleep disturbance is not mentioned

Five appendices include normal values drug dosages, fluid and electrolyte needs blood taking, and how to do a cut down Commonly available growth charts ar generously allotted 15 pages. Despite bein barely large enough to use, they are infinitely preferable to tables of anthropomorphic data.

In two situations only could one fin contentious advice: hyposensitisation i recommended in favour of systemic antihistamines and in suspected meningiti and established coma no warning is give about the danger of coning in the absenc of papilloedema. This is a distinctly usefu addition to many a houseman's pocket, an at an affordable price, therefore I shall b recommending it to my junior paediatri staff.

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*Archives of Disease in Childhood,* 1989, **64,** 769

## *British Paediatric Association*

# British Paediatric Association Diamond Jubilee Service

The British Paediatric Association celebrated its Diamond Jubilee with a service of thanksgiving in Westminster Abbey on 12 October 1988. The Right Reverend and Right Honourable Lord Coggan, a former Archbishop of Canterbury, gave a very moving address with messages that are pertinent to us all. He has kindly consented to the reproduction of the following extracts in order that others may share his words and thoughts.

If I were a parish priest—and after all, they do the basic work of the Church's ministry while we bishops get all the publicity and the brickbats!—I would want to have a staff meeting which met regularly. By staff, I would have in mind not only my curate, church wardens, and organist. I would want the local policeman, school teacher, welfare officer and—yes—perhaps most important of all, the local general practitioner. Why? Because we are, everyone of us, clergy and these experts in their various fields, all engaged on one great task—the health, wholeness, and holiness of the community. How better can that be put than it was in your fine book *Child Health in a Changing Society:* 'Health is well-being in its *widest* sense; disease is deviation . . . from that optimum state'. Only when our skills are combined can a proper local health operation be launched and carried through.

This evening, at Marylebone Parish Church, they are dedicating to the service of God and of his people a healing and counselling centre. It is the result of a remarkable vision. The huge crypt of that church, hitherto used as a burial place, has been turned into a very lively place where the healing ministry of the Church joins hands with the practitioners of the various branches of medicine—Harley Street is just nearby—and with the healing forces of music—the Royal College of Music is a stone's throw away. In recent decades, the Church has been reawakening to her original commission to heal the sick. She obeys that commission not in opposition to or in competition with the scientists and doctors who steadily pursue their skilled professions, but in closest cooperation with them, seeing their expertise as a gift from God the Lord of all life.

When we have a child before us—you in your clinic or surgery, or the priest in his study or vestry—we are concerned with that child's total welfare, his 'wholeness'. He may have some deficiency which can be easily remedied, some accident the results of which can soon be put right. But, on the other hand, he may be, so far as we can detect, physically well—and yet not be whole. Concealed behind that brave exterior may be a distorted mind, a wounded spirit, a twisted personality, and we are concerned with the total welfare of the *person.*

We recognise the damage which comes to a child when he is born into poverty, with inadequate nourishment, with insanitary conditions, with overcrowding and little opportunity for sport. There are pockets of these things even yet in our society. But at the other end of the social scale, there can also be starvation, a starvation of love, of parental supervision and expenditure of time with the child, and the presence of an atmosphere which says 'Money and success are all that matters. Go for your rights and you can forget your duties. Look after number one and forget about God and neighbour'. Where children are brought up in homes like these, damage is done to their wholeness which often proves irreparable.

My own doctor, who has great experience in dealing with schoolchildren, recently emphasised to me the importance of listening, and listening patiently, to the child before him. He must not be fobbed off with a bottle of medicine. He has a burden on his mind which, perhaps, he finds it difficult to express; and, however hard it must be when there are others waiting for our attention, that child must be given the chance to get his burden off his chest and have the privilege of a listening and understanding ear. We need an army of listeners.

*Archives of Disease in Childhood,* 1989, **64,** 770

# *Neonatology—then and now* *(C H M Walker)*

## Kernicterus (1957)

# Kernicterus not associated with haemolytic disease

W H BOON

*The General Hospital, Singapore (Arch Dis Child* 1957;**32:**85–90)

This paper describes the features of 26 cases of kernicterus not associated with haemolytic disease of the newborn, a topic of growing interest at the time. Contrary to the usual experience in which such cases are found mainly in premature babies, all but two (four unknown) were born at full term. Jaundice was noted within 48 hours in more than half and the clinical indications of brain damage included drowsiness and muscular hypertonicity, though only two had fits. There was a high mortality, 15 of the 20 who died doing so within the first week. The discussion begins with a debate as to whether or not kernicterus is caused by bilirubin fixing in injured tissues or invading otherwise normal brain cells. Much is made of the fact that where predisposing factors are concerned the newborn seems able to tolerate profound hypoxia without sequelae and that exchange transfusion seems to provide considerable protection. Thus the conclusions were:

> 'The argument that premature babies are more prone to kernicterus than full-term infants due to their greater liability to cerebral anoxia and hence brain damage is not really tenable'.
>
> And later 'It is therefore more likely that bilirubin or its products in excessive amounts in the blood are deposited in the brain tissue and cause injury directly.'

The author also considered that the basis of the hyperbilirubinaemia may well have been poorly nourished newborn babies as a result of maternal protein malnutrition with, in some cases, superadded infection.

**Today** Non-haemolytic jaundice in the newborn is still a serious problem in many parts of the world and the risk of kernicterus is ever present, especially in the preterm infant. While high concentrations of bilirubin can perhaps by themselves injure brain cells there are reports of babies (usually born at full term) with extremely high values who never show clinical evidence of kernicterus. It is now generally accepted that additional factors such as hypoxia, acidosis, hypoglycaemia, and hypothermia are frequent precursors and it is therefore not surprising that kernicterus has been found in preterm babies with bilirubin concentrations as low as 140 μmol/l.

Where adequate monitoring and treatment are available the neurological sequelae of kernicterus must now be rare in infants born at full term. It would seem, however, that up to 10% of low birth weight babies may still be found to have a lesion at necropsy ('silent' or otherwise) with concentrations as low as 140 μmol/l. Since the association between bilirubin concentrations and neuropathology is not linear it is difficult to decide which of the several aetiological factors is most responsible, particularly when many of the later findings in the central nervous system of the preterm baby are not of the bilirubin toxicity type.[1]

Specific tests for bilirubin encephalography, such as brain stem evoked responses for deafness, are required in carefully controlled long term studies if this uncertainty about kernicterus is to be resolved. Meanwhile the protective effect of exchange transfusion, which I respectively submit to have been erroneously considered to indicate the irrelevance of additional factors, should probably be offered at considerably lower concentrations in preterm babies. Whether it is more effective to give phototherapy prophylactically or to wait until the bilirubin concentration has reached about 150 μmol/l is still uncertain but such treatment has been shown to reduce the need for the more hazardous exchange transfusion.

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Wong Hock Boon, Professor and Foundation Chairman, Department of Paediatrics, National University of Singapore, is one of Asia's foremost paediatricians. The paper chosen above is indicative of his early interest in neonatal jaundice and he has been instrumental in the virtual eradication of mental retardation due to jaundice caused by glucose-6-phosphate dehydrogenase deficiency in Singapore. His other clinical contributions include work on haemoglobinopathies, eosinophilic purpura, infectious mononucleosis, and marrow transplantation.

He has played a principal part in Singapore Ministry of Health Committees (Immunisation, Medical Advisory and Clinical Research) and has, from 1979, been Chief of the World Health Organisation Collaborating Centre for Research and Training in Human Genetics.

His contribution to paediatric writing has been quite exceptional in that he has written numerous books, contributed to many others, and has a most extensive bibliography. He has been editor or a member of the editorial board of more than 10 journals.

It is not surprising that in addition to Gold Medal and Meritorious Service awards he has more recently received the Most Outstanding Paediatrician in Asia (1986), and Inaugural Science and Technology (1987) Awards.

7·11, 7/c

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## *Annotation*

# Congenital heart disease in the adolescent

Congenital heart disease occurs in approximately 1 in 100 births. Left to nature 60% would die in infancy, 25% in the newborn period, and probably only 15% would survive to adolescence and adult life.[1] Since Gross and Hubbard (1938) ligated the duct,[2] Craaford and Nylin (1945) resected coarctation of the aorta,[3] and Blalock and Taussig (1945) with their shunt changed the fortunes of children with cyanotic congenital heart disease,[4] surgical treatment has advanced so that most lesions can be repaired or palliated and no age is too young for cardiac surgery. Whether some of the newer procedures for hypoplastic left heart and other complex malformations are advances or retrograde steps in terms of suffering and survival remain to be evaluated.

Challenged by the surgeon, the art and science of preoperative diagnosis and care developed. As the major problems presented in infants and neonates, paediatricians were inevitably involved. Thus the specialty of paediatric cardiology was born and grew in strength to maturity, celebrated in its own World Congress held in London in 1980 where the problems of adolescents were specifically addressed in the final plenary session on Adolescent Survivors—Triumphs or Disasters?[5] The prospect for survival to adult life to become a wage earner and enjoy family life is now available for the child born with serious congenital cardiac anomalies.

Is the concept of 'total correction' really true? In terms of 'excellent' and good results, do these patients need care, support, or further surgical treatment when they reach adolescence* or adulthood? The answer is that many do even though many lead normal lives.[6] How many 'grown up' people with congenital heart disease are there in the United Kingdom and how many need help or further surgery? Certainly they are increasing in number each year.

The National Heart Hospital in 1976 extended inpatient facilities to cope with increasing numbers of adolescent cardiac patients by opening a paediatric and adolescent unit. These young patients usually like to be with their own age group. Depending on sexual maturity and preferences some may wish to be in adult wards. It is surprising that many of the young adults into their 20s or 30s prefer to stay with the young rather than be with the older adult cardiac patients. The National Heart Hospital has accepted the commitment to the growing up of congenital heart patients and established a service for their special problems both as inpatients and outpatients, for long distance national consultations, and for further specialised surgical expertise. A total of 94% of adolescent cardiac admissions have congenital heart disease and 75% have had cardiac surgery in childhood or infancy.

Hospital beds continue to be needed for adolescents with cardiological problems. Arrhythmias precipitate the need for admission most commonly in the medical patients and this includes recurrent pacemaker changes. Pacing may be difficult because of shortage of venous access or odd anatomy. Arrhythmias in this group are often complex requiring expert management and electrophysiological knowledge and investigation. Care is required not to administer drugs that cause deterioration in myocardial function of the already abnormal ventricle upon which systemic output depends. Endocarditis, progressive pulmonary vascular disease, myocardial dysfunction, and effects of lung infections require inpatient treatment. The diagnosis and referral of infective endocarditis is frequently late, not only in adolescents but also in older patients, not because of delay in consultation but because of lack of thought of the diagnosis by practitioners. Aware of the need for prevention in a 'card carrying' or scarred young patient, doctors continue to prescribe antibiotics for non-specific symptoms without appropriate prior blood tests and cultures. This results in delayed diagnosis and blood culture negative endocarditis with a worse prognosis and greater destruction than if the diagnosis had been correctly sought and confirmed early. This is inexcusable in those with known congenital heart disease, who have already been operated on, and where the risks are clearly spelt out. Adolescents may be reluctant to consult doctors. After a serious complication they often bypass local help and come directly to the centre where they feel 'their hearts are understood'. The service has been designed so that patients and their physicians can easily make telephone contact and through the unit data base, with about 3500 patients indexed and followed up, there is instant information available. This has helped in the management of many questions and difficulties relating to depression, threatened suicide, prison sentences, unwanted pregnancy, demands of unusual life style, and employment without having to first seek notes.

---

*For convenience and ease this refers to patients aged 12–19 years but there are no absolute limits for the start or finish of adolescence! It is different for girls and boys.

In the last five years demands for adolescent cardiac beds have changed; there is less demand now for invasive investigation, which has been replaced by non-invasive outpatient investigation, but there is more demand for interventional procedures and assessment for heart and heart/lung transplantation. This is a courageous group of young people, costly to investigate and maintain, and demanding of many support services. Looking after them while they are waiting for a heart presents many medical problems as well as social problems and demands for psychological support, which must be addressed by the adolescent/young adult unit once the assessment is completed.

The cardiac surgeon's skills are needed for reoperations, particularly to replace valves and conduits used in the initial 'correction' (better considered as radical repairs). Natural valves, particularly the aortic valve, may degenerate and calcify after earlier valvotomy or become critically narrow in the second decade. Complex congenital defects, previously helped by extracardiac palliation, damage by endocarditis, and residual lesions claim surgical attention. There are different problems than at the first operation and parents are often unprepared for the need, morbidity, and fatalities of reoperation. Interventional techniques may reduce some of the surgical needs but still the reoperation risks are increased and should be dealt with by the most experienced and cautious. Too many deaths have occurred during reopening by an unwary or inexperienced junior surgeon. The surgical management of 'grown up' congenital heart disease urgently requires rationalisation. It is not for the general adult cardiac surgeon to 'have a go'.

These problems in the adolescent cardiac patients continue in the adult 'until 70'. The problems of acquired ischaemic heart disease and hypertension are added to the abnormal heart with each added decade. In addition, the requirements of these young patients with congenital heart disease for advice on life's normal problems such as contraception, employment, insurance, prison confinement, marriage, pregnancy, and risks of affected offspring, and whether it is safe for them to hold an 'until 70' driving licence or vocational licence are a demanding part of outpatient work. Special advice is often needed about extracardiac surgery, trauma, and accidents. When advice is not sought, nor given by the informed, the patient's life may be at risk.

## Who knows and who cares?

The problems of the adolescent with congenital heart disease continue into adult life. The National Heart Hospital statistics show not only an increase in adolescent referrals but also a rise in inpatient admissions of patients over 20 and 30 years with problems related to treated congenital heart disease. It should be accepted that most of these patients require someone with knowledge to continue their long term supervision and be available for consultation in respect of the problems that confront teenagers and adults.[7] Perloff is facing the same problems in the United States and is trying to establish a programme for the care of these patients.[8] There are some patients with treated lesions such as ligated ducts (also sectioned ducts), closed atrial septal defects, and most of those with mild pulmonary valve stenosis and pulmonary valvotomy in whom regular or even any informed supervision is unnecessary. In most treated congenital heart disease, particularly the cyanotic and complex, good medical supervision is important for their maintained well being. Even simple atrial septal defects may develop fast atrial rhythm disorders 10–20 years after the successful surgery and this can carry an embolic risk.

Paediatricians and paediatric cardiologists must accept the need not only to make proper referral arrangements but also to indoctrinate the patient and family about importance of continuing informed medical supervision. The age when it is necessary to refer to a 'grown up' clinic varies according to the cardiological demands, local expertise, and maturity of the patient. The time must be recognised when the child no longer wants the tripartite relationship with parent and paediatrician but wants the one to one adult relationship with the doctor. This problem often causes resentment with refusal to attend clinics. Adolescents are naturally rebellious in their pursuit of independence. Whoever or wherever the patient is cared for, it must be realised that it is for longer than adolescence and includes the life span. Having accepted the need, the arrangements and implementation are sometimes difficult. At the present time flexibility is vital.

In some centres with close proximity (and good relations) between paediatric and adult cardiologists, joint clinics can be organised. Many, including the patient, feel the paediatric cardiologist should continue the care but often it is not practical, as he or she does not have access to adult beds or knowledge of adult acquired heart diseases. On the other hand, the cardiologist trained in coronary and valvular disease is ignorant and even fearful of congenital heart disease, particularly when complex. There may be particular problems when the paediatric cardiac surgical centre is in a children's hospital that is separate in location and in philosophy from its adult counterpart. Forward looking arrangements must be organised as growing up is certain for childhood successes and survivors. Just as the need for treatment of neonatal and infant cardiac patients in specialist supraregional centres was recognised by the Department of Health and Social Security,[9] so I believe special arrangements should be made for the grown up congenital heart patients. There will soon be more of these than infants.

The ROCK philosophy must be implemented:

**R**ecognise that there is a problem that requires attention and that most physicians are ignorant in this field.

**O**rganise formal follow up and supervision for patients by someone or a group who are familiar and interested.

**C**entralise patients with informed cardiologists and surgeons experienced in the problems of congenital heart disease. A supraregional concept may be necessary in planning, preferably where there are designated inpatient facilities for the young to stay together. They usually like it and prefer to be with young rather than with older cardiac cases involving failure, strokes, etc.

**K**nowledge is vital. Special education and training, but not in neonates, is important. Experience in reoperation and basic anatomy and pathology of congenital heart disease is mandatory for surgeons involved.

The problems of long term care must apply to other childhood diseases. Paediatricians must accept that their successful treatment has produced a new medical community beyond the age of their specialist competence. It should not be difficult to solve once the problem is recognised, provided consultants are not rigid in their intellectual practices and are willing to share their skills and facilities. These patients have been through much in cost, time, endeavour, and courage. They deserve to be maintained as productive members of society. Today's problems may be different from tomorrow's but it is certain there will be as many or more into 2000 AD until the occurrence of congenital cardiac and cardiovascular malformations is reduced or even abolished. Regions, supraregions, and even the Department of Health could usefully address the problem—it has much wider implication than for the survivors of congenital heart disease.

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*Archives of Disease in Childhood,* 1989, **64,** 774–779

## *Original articles*

# Acute duodenal ulcer

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SUMMARY A series of 31 infants and children with acute duodenal ulcer verified by endoscopy was studied over an eight year period. Eighteen (58%) of them were under 2 years of age. The most common symptom was upper gastrointestinal bleeding (n=27, 87%). Twenty nine patients (94%) had a preceding illness characterised by diarrhoea, upper respiratory tract infection, or fever, which was not necessarily treated with antipyretic drugs. Initial endoscopy showed that ulcer lesions were solitary in 14 patients and present on the anterior wall (n=11), posterior wall (n=2), or both (n=1). Multiple ulcers were found in 17 patients, and present in the bulb with (n=6) or without (n=11) extension into the second part of duodenum. The most conspicuous finding was the irregularly shaped ulcers seen in eight young children with similar clinical and endoscopic features. Sixteen patients were re-endoscoped one to two weeks after the initial examination; the ulcers had entirely disappeared in 13, and there were only small residual ulcers in three. Thirty patients were treated medically and only one (with uncontrollable haemorrhage) required operation. Most patients were symptom free two to six years after the initial diagnosis.

Our results suggest that young children may develop acute duodenal ulcers after viral illnesses whether or not they are treated with drugs, mainly antipyretics. This kind of acute duodenal ulcer usually heals quickly irrespective of the morphology, site, and number of ulcers.

Acute peptic ulcer in infancy and childhood occurs in many diseases; these include spontaneous ulceration in neonates, Cushing's ulcer in diseases of the central nervous system, 'stress' ulcer, and drug induced ulcer—for example, after taking steroids.[1] A review of published reports showed that most acute peptic ulcers in infancy and childhood were diagnosed by barium meal study, or at laparotomy, or even necropsy.[1-7] Radiographic studies may fail to show an acute duodenal ulcer because it is usually superficial, either causing no deformity of the duodenal wall or located on the anterior wall of the bulb.[8] On the other hand, there may be false positive results if the duodenal bulb is spastic or irritable during a barium meal study.[9] These problems are virtually non-existent with endoscopy, which has replaced barium examination during the last decade and is now the examination of choice in infants and children with gastrointestinal diseases.[10-12] The evolution of endoscopic features during the course of acute duodenal ulceration in childhood, however, has to our knowledge never been described. Additionally, so that we may better understand the pathogenesis of acute duodenal ulcer, more clinical information is needed. We began to use endoscopy in children under 6 years of age in this large referral hospital in 1977,[11] and since then we have identified 31 patients with acute duodenal ulcer, which was clearly a different entity from chronic duodenal ulcer. This paper investigates the clinical and endoscopic features seen at the initial visit and during follow up in these 31 patients.

## Patients and methods

Thirty one children (24 of whom were boys), aged 2 days to 14 years, were seen in the department of paediatrics at the National Taiwan University Hospital between September 1978 to December 1986 and identified at endoscopy as having acute duodenal ulcers. Their clinical details including sex, age, symptoms and signs, preceding illnesses and drugs, associated diseases, and family history were recorded. All the patients underwent panendoscopic examination at the time of presentation. Follow up endoscopy was undertaken in 16 patients one to two weeks after the initial diagnosis. The endoscopes used were the Olympus GIF-$P_2$ or GIF–XP. Patients were asked to fast for eight hours before endoscopy and premedication consisted of pethidine (2 to 2·5 mg/kg) and hyoscine butylbromide (0·4 to 0·5 mg/kg) by intramuscular injection 20 to 30 minutes before the procedure. For uncooperative patients, diazepam (0·5 to 1·0 mg/kg) was given intravenously before the examination.

Patients who had recurrent or long standing digestive symptoms (more than one week) or who had initial endoscopic features showing convergent folds, deformity of the duodenal bulb, or other signs suggestive of chronic ulceration were excluded from the study.

After endoscopy, the number, size, shape, sites, activity, and surrounding reaction of ulcers were recorded. Biopsy specimens were taken from the edges of duodenal ulcers if there were any unusual endoscopic features.

All the patients were initially managed conservatively with antacids ($n=26$), cimetidine ($n=3$), or sucralfate ($n=2$). Patients were closely observed and a surgeon consulted if bleeding continued or if other complications were noted.

Follow up took place in the gastrointestinal clinic. Patients who failed to return were interviewed by telephone or letter. Information was requested concerning the frequency, duration, and characteristics of digestive symptoms after the diagnosis and treatment of acute duodenal ulceration.

Fasting serum gastrin concentrations were measured regularly by radioimmunoassay (Biodata Gastrin Kit), and the antibody used in the kit had 100% specificity for gastrin G17 and 58% specificity for gastrin G34. The results were expressed as pg/ml.

Fisher's exact test was used for statistical comparisons.

## Results

Twenty four boys (mean age 3·2 years) and seven girls (mean age of 3·3 years) were studied. Eighteen (58%) were under 2 years of age, five (16%) were aged 2 to 4 years, 3 (10%) were aged 5 to 6 years, and five (16%) were aged 7 to 14 years (table 1).

A preceding fever was more common among patients under 4 years of age ($p<0\cdot05$). Although the incidences of other preceding events were not significantly different between the age groups, diarrhoea or upper respiratory tract infection seemed to occur more often in younger patients. Among the eight patients under the age of 4 years who had previously been taking antipyretic drugs, six had taken aspirin, one had taken paracetamol, and one had taken another non-aspirin preparation; the dosages were all within the therapeutic range. Abdominal pain was much less common among younger children ($p<0\cdot05$). Though melaena occurred more often in patients under 4 years old ($p<0\cdot05$), haematemesis was more common in older children. Upper gastrointestinal bleeding was the most common sign, occurring in 87% of our cases. Only two patients had a family history of peptic ulceration.

Twenty nine patients (94%) had a preceding illness characterised by diarrhoea ($n=15$), upper respiratory tract infection ($n=7$), or fever ($n=20$); 14 patients had been given drug treatment before the onset of upper gastrointestinal bleeding. In two

Table 1 *Clinical features in patients with acute duodenal ulcer in two age groups. Figures expressed as number (percentage)*

| | *Patients aged 4 years or less ($n=23$)* | *Patients aged 5–15 years ($n=8$)* | *p Value* |
|---|---|---|---|
| Sex: | | | |
| Male | 18 (78) | 6 (75) | $>0\cdot05$ |
| Female | 5 (22) | 2 (25) | $>0\cdot05$ |
| Symptoms: | | | |
| Fever | 18 (78) | 2 (25) | $<0\cdot05$ |
| Diarrhoea | 13 (57) | 2 (25) | $>0\cdot05$ |
| Upper respiratory tract infection | 7 (30) | 0 | $>0\cdot05$ |
| Drugs: | 11 (48) | 3 (38) | $>0\cdot05$ |
| Antipyretics | 8 (35) | 1 (12) | $>0\cdot05$ |
| Others | 3 (13) | 2 (25) | $>0\cdot05$ |
| Family history of duodenal ulcer | 1 (4) | 1 (12) | $>0\cdot05$ |
| Vomiting | 5 (22) | 2 (25) | $>0\cdot05$ |
| Haematemesis | 7 (30) | 4 (50) | $>0\cdot05$ |
| Melaena | 20 (87) | 2 (25) | $<0\cdot05$ |
| Abdominal pain | 1 (4) | 4 (50) | $<0\cdot05$ |

cases there was no preceding illness and their ulcers were diagnosed only because one had abdominal pain (a 5 year old boy) and the other had dark reddish stools (a 2 day old newborn). Investigation of those patients in hospital subsequently showed the following coexistent illnesses: salmonellosis (n=2), hypothyroidism (n=1), methylmalonic acidaemia (n=1), Meckel's diverticulum (n=1), roseola infantum (n=1), oesophageal candidiasis (n=2), pharyngoconjunctivitis (n=1), Kawasaki disease (n=1), anaphylactic purpura (n=1), and tuberculous meningitis (n=1).

### ENDOSCOPIC FEATURES

Table 2 shows that at initial endoscopy ulcers were solitary in 14 patients, and distributed over the anterior wall (n=11), posterior wall (n=2), or both (n=1). Multiple ulcers were found in 17 patients and located at the bulb with (n=6) or without (n=11) extension into the second part of duodenum. Sixteen patients were re-endoscoped one to two weeks after the initial endoscopy. The ulcers had entirely disappeared without scar formation in 13, and left as only tiny residual ulcers in three patients.

A comparison of clinical features of patients with multiple and solitary ulcers (table 3) shows that the mean age, the incidence of predisposing factors and clinical symptoms, and of a positive family history,

Table 2 *Endoscopic features of 31 patients with acute duodenal ulceration*

| | *Single ulcer* | *Multiple ulcers* |
|---|---|---|
| **At initial endoscopy** | | |
| No of patients | 14 | 17 |
| Location of ulcers: | | |
| Anterior bulb | 11 | 2 |
| Posterior bulb | 2 | 0 |
| Both anterior and posterior bulb | 1 | 9 |
| Bulb and second part | 0 | 6 |
| **At follow up endoscopy** | | |
| No of patients | 8 | 8 |
| No of healed ulcers | 6 | 7 |
| No of small residual ulcers | 2 | 1 |
| **Associated features** | | |
| Superficial gastritis | 1 | 1 |
| Haemorrhagic gastritis | 2 | 2 |
| Oesophageal ulcer | 0 | 3 |

Table 3 *Comparison of clinical features of patients with single ulcers and those with multiple ulcers*

| | *No with single ulcer (n=14)* | *No with multiple ulcers (n=17)* |
|---|---|---|
| Sex (M:F) | 10:4 | 14:3 |
| Mean (SD) age years | 2·7 (4·2) | 3·6 (3·5) |
| Symptoms: | | |
| Fever | 7 | 13 |
| Diarrhoea | 6 | 9 |
| Upper respiratory tract infection | 3 | 4 |
| Drug treatment | 6 | 8 |
| Vomiting | 1 | 6 |
| Abdominal pain | 1 | 4 |
| Haematemesis | 3 | 7 |
| Melaena | 12 | 10 |
| Family history of duodenal ulcer | 1 | 1 |
| Haemoglobin concentration <80 g/l | 7 | 4 |

None of the differences are significant.

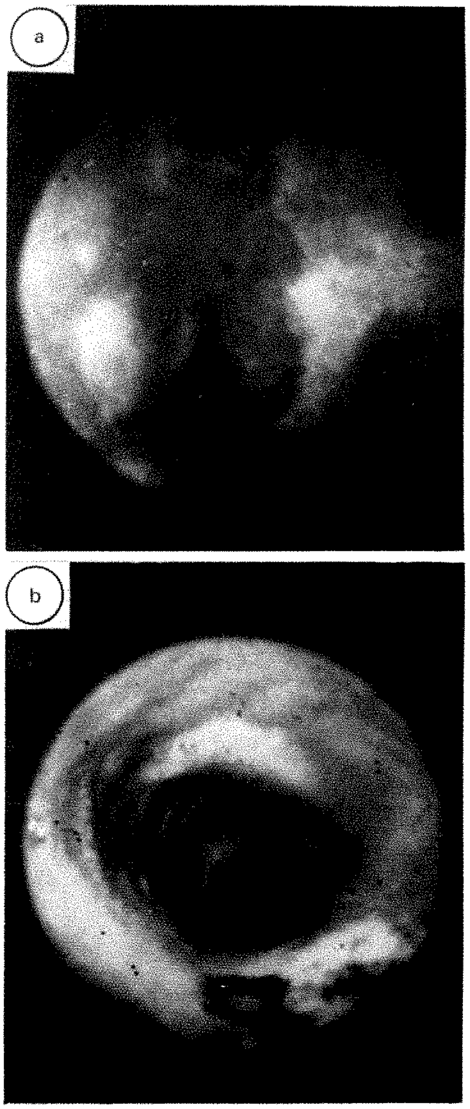

Figure *Endoscopic appearance in a 3 year old boy with irregularly shaped ulcers at (a) the duodenal bulb and (b) in the second part of duodenum.*

were similar in both groups. Analysis of the haemoglobin concentration at the initial presentation shows that the single ulcer group tended to have a higher incidence of profound anaemia (haemoglobin concentration <80 g/l) than the multiple ulcer group, although there were no significant differences between the two groups.

With respect to the endoscopic morphology of the ulcer lesions, eight cases with irregularly shaped ulcers were identified.

The endoscopic features of the ulcers in these patients were: that they were multiple and shallow, they varied in size from pinhead to several cm, they were well demarcated and irregularly shaped, they were distributed over the whole bulb (with or without extension into the second part), and they healed rapidly—usually within two weeks of the initial bleed (figure a and b, table 4). Patients with irregularly shaped ulcers received antipyretic drugs more often than those whose ulcers had smooth outlines: seven of eight patients with irregular ulcers received antipyretic drugs compared with two of 23 patients with smooth ulcers ($p=0{\cdot}0002$). Thus the use of antipyretic drugs resulted more often in irregularly shaped ulcers, especially in those under the age of 4 years.

### TREATMENT AND FOLLOW UP

Thirty patients recovered after conservative treatment without complications. Only one boy aged 22 months who had multiple ulcers in the duodenal bulb developed uncontrollable haemorrhage, and finally required laparotomy, haemostasis, and pyloroplasty.

There have been no instances of recurrent ulcers in the two to six year period since the initial diagnosis.

### SERUM GASTRIN CONCENTRATIONS

Gastrin analysis was performed in 11 patients. The ranges of their fasting serum gastrin concentrations were 36·2–58·5 pg/ml for two patients with solitary duodenal ulcers, 13·3–88·3 pg/ml for five patients with multiple duodenal ulcers confined to the bulb, and 26·4–69·9 pg/ml for four patients with multiple ulcers that extended from the bulb into the second part. Gastrin measurement could not be performed in the remaining patients who were either enrolled before the assay was available, or did not provide sufficient serum for analysis. The observed range of fasting serum gastrin in normal Chinese children using the same method were 40–183 pg/ml in 30 infants aged 2–6 months, 36·5–110 pg/ml in 14 infants aged 7–12 months, 20·5–140 pg/ml in 23 children aged 1–2 years, 13·7–189 pg/ml in 97 children aged 3–5 years, 12–111 pg/ml in 17 children aged 6–9 years, and 5·3–97·6 pg/ml in 32 children aged 11–15 years.

Table 4 *Clinical and endoscopic features of eight patients with irregularly shaped ulcers in the duodenum*

| | *Case No* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* |
| Age | 1 year 10 months | 1 year 2 months | 3 years 10 months | 1 year 4 months | 2 years | 11 months | 4 months | 10 months |
| Sex | Female | Male | Male | Male | Male | Male | Male | Male |
| Prodromal symptoms: | | | | | | | | |
| Fever | Moderate | High | High | Mild | None | High | High | High |
| Vomiting | Yes | Yes | No | Yes | Yes | Yes | Yes | No |
| Diarrhoea | Yes | Yes | No | Yes | Yes | Yes | Yes | No |
| Conjunctivitis | No | No | Yes | No | No | No | No | No |
| Cough and rhinorrhoea | No | No | Yes | No | No | Yes | No | No |
| Haematemesis | No | No | Yes | No | Yes | Yes | Yes | Yes |
| Tarry stool | Yes | Yes | Yes | Yes | No | No | No | Yes |
| Duration between onset of symptoms and upper gastrointestinal bleeding (days) | 2 | 3 | 2 | 1 | 7 | 3 | 2 | 1 |
| Receiving antipyretic drugs | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Haemoglobin concentration on admission (g/l) | 90 | 65 | 122 | 55 | 120 | 128 | 70 | 110 |
| Location of ulcers: | | | | | | | | |
| Anterior wall | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Posterior wall | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Second part | Yes | No | Yes | Yes | Yes | No | Yes | No |
| Associated illness | None | None | Pharyngo-conjunctivitis | Salmonella enteritis | None | Oesophageal ulcer | None | Roseola infantum |
| Histological appearance of biopsy specimen | Duodenitis and erosion | Not done | Duodenitis and erosion | Duodenal ulcer | Duodenitis and erosion | Duodenitis and erosion | Not done | Not done |
| Blood transfusion | Yes | Yes | No | Yes | No | No | Yes | No |

## Discussion

There were 29 patients (94%) in whom a preceding illness such as fever, upper respiratory tract infection, or gastroenteritis were present. In addition, 12 patients (39%) also had various associated underlying diseases of differing severity as predisposing factors. This suggests that most of the acute duodenal ulcers in the series were secondary, with a preceding illness or identifiable underlying diseases which acted as a non-specific stressful episode and potentially predisposed to the acute type of ulcer development. No methods exist, however, to quantify this stress, and it could be argued that in some of the cases, acute duodenal ulcers may have been directly related to infection. Supporting evidence may be in that *Candida albicans* was isolated from oesophageal ulcers in two patients who had apparently similar ulcers in both duodenum and oesophagus. Thus the relation between infection and acute duodenal ulcer may be analogous to that between antral gastritis and *Campylobacter pylori,* which is interesting, but still controversial. Catastrophic predisposing factors such as trauma, sepsis, operation, burns, or diseases of the central nervous system (except the one case of tuberculous meningitis) were rarely seen in this series, because patients in these categories were too ill to permit endoscopic evaluation. This is different from previous reports mostly from surgical units whose patients required surgical intervention.[1-4]

Other predictive features such as age and sex as well as the commonest symptoms are in agreement with those of earlier studies.[1-3 5] Recent observation in our children with chronic duodenal ulcers has shown that 60% of the patients had family members affected by peptic ulcer diseases.[13] It is consistent with a previous study on predisposing factors in childhood duodenal ulcers.[14] Lack of positive family history in this series probably reflects that genetic predisposition plays little part in the pathogenesis of acute duodenal ulcers. Most of our patients also lived in urban areas or other neighbourhoods with high population density. They were theoretically more likely to be infected by various viral agents than those in rural areas, resulting in febrile illness and predisposing to the development of acute duodenal ulcers. We were unable, however, to conclude that there is geographic predisposition in acute duodenal ulcers because a nationwide survey for peptic ulcer diseases has not yet been performed. On the other hand, we see fewer cases of acute duodenal ulcers than previously, probably because paracetamol is used more and aspirin is used less.

Curci *et al,* Krasna *et al,* and Dunn *et al* have all showed that most of the acute peptic ulcers found at necropsy and at laparotomy were solitary.[1 15 16] This study, on the contrary, showed that multiple lesions in acute duodenal ulcers in childhood were common. Furthermore, solitary ulcers often occurred on the anterior wall of the duodenal bulb, and multiple ulcers extending from the bulb into the second part of duodenum were not rare. Indeed, fasting serum gastrin concentrations were within normal limits in the later four patients with extending multiple ulcers. This together with the lack of recurrence indicate that the Zollinger-Ellison syndrome is not a likely diagnosis in these patients. The stress or secondary ulcer is often shallow without induration, and difficult to recognise radiologically.[5] Endoscopy provides the best visualisation of the shape, number, and distribution of acute duodenal ulcers.

Follow up endoscopy in 16 patients has shown that acute duodenal ulcers in childhood after viral illness with or without treatment with antipyretic drugs often healed within one to two weeks of the initial bleed irrespective of the morphology, size, site, and number of the ulcers. Endoscopic and clinical follow up of these patients also suggests that, in contrast with chronic duodenal ulcers, acute duodenal ulcers are usually self limiting without recurrence, and follow up endoscopy may be unnecessary. Operation has been commonly considered the treatment of choice for serious complications of acute peptic ulcer in childhood, such as uncontrollable bleeding or perforation.[1-3 5 6] Only one of our patients required operation, and this shows the less serious problems with acute duodenal ulcers in this series in striking contrast with the serious outcome of stress ulcers often seen in other critically ill patients. Moreover, conservative management of the patients with acute duodenal ulcers was successful by short term treatment with antacids, $H_2$ receptor antagonists or a mucosal cytoprotector alone. No patients relapsed, which usually occurs in children with chronic duodenal ulcer once treatment has been stopped.[13]

Perhaps the most interesting endoscopic features of this series, not previously reported, is that of the irregularly shaped ulcers seen in eight patients. These patients shared common clinical features: they were infants or toddlers, they had had a viral illness with fever, antipyretics had been given before upper gastrointestinal bleeding had occurred, and they did not recur after a long period of follow up. The endoscopic lesions in these eight patients also had common characteristics, as shown in the results.

Aspirin is known to be associated with gastric ulcer, but the causal relation between aspirin and duodenal ulcer remains uncertain.[17] We have recently encountered 16 patients with acute gastric ulcers. Seven of them also had a history of taking antipyretic drugs, but none had irregularly shaped ulcers.[13] In this series, infants with irregularly shaped ulcers often were fasted by their anxious mothers when they had acute diarrhoea. Starvation, plus a viral illness or its related stress, probably enhance the likelihood of developing acute duodenal ulcers when ulcerogenic drugs like aspirin were also given. Ament described a case with a small superficial lesion like an aphthous ulcer in the second part of the duodenum.[10] Krasna *et al* and Rosenlund *et al* reported cases of childhood duodenal ulcers confined to the second part of the duodenum.[15 18] Their cases differed from ours, who showed irregular ulcers both in the bulb and extending to the second part. As these eight and the other patients in the present series showed similar courses both clinically and endoscopically, it is premature to draw a conclusion that these irregular ulcers may implicate any particular form of acute duodenal ulcers in early childhood.

In summary, the present results are at variance with previous reports in showing that acute duodenal ulcers in childhood often appear as multiple lesions, may be irregularly shaped, and may extend into the second part of duodenum. These acute ulcers are generally benign with rapid healing, and do not relapse. Febrile illnesses of viral or other origin, often in combination with ulcerogenic drugs, frequently preceded upper gastrointestinal bleeding. The mechanisms by which these preceding events produce acute duodenal ulceration requires further study.

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# Gastro-oesophageal reflux in preterm infants

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SUMMARY Gastro-oesophageal reflux in very low birthweight infants was studied using a new 1 mm monocrystalline antimony oesophageal pH electrode. Gastro-oesophageal reflux was detected in 30 (85%) subjects. The mean (SEM) number of episodes of reflux in 24 hours was 12·1 (2·1), and 3·2 (0·6) lasted over five minutes. The mean reflux index was 4·5 (1·0)%, and the longest episode 17·1 (4·6) 17·1. Reflux was unrelated to postconceptional age or to resting lower oesophageal sphincter pressure. The mean reflux index was low at rest before feeds, being 1·8 (0·6)%, and increased slightly after feeds (3·8 (1·0)%), but was significantly increased after nursing care to 16·4 (3·0)%, and while xanthines were being given (5·9 (1·6)%. A subgroup of seven infants with xanthine resistant apnoea had severe gastro-oesophageal reflux that was not clinically apparent (reflux index 27·4 (3·6)%). Successful treatment of the reflux (reflux index: 3·6 (1·2)%) was associated with cessation of the apnoea.

We conclude that gastro-oesophageal reflux is common, and is usually not clinically apparent, even when severe. It is important to consider gastro-oesophageal reflux in the differential diagnosis of xanthine resistant apnoea in preterm infants.

In preterm infants gastro-oesophageal reflux and subsequent pulmonary aspiration of gastric contents has been suggested as a complication of early feeding[1 2] and has led to a cautious approach to the early introduction of enteral feeds. Gastro-oesophageal reflux has also been implicated in the pathogenesis of chronic respiratory problems such as bronchopulmonary dysplasia,[3] and in the aetiology of apnoea and sudden infant death syndrome.[4] In very low birthweight (VLBW) enterally fed, preterm infants receiving modern intensive care, however, the incidence, severity, and clinical importance of gastro-oesophageal reflux are not known.

We have therefore studied a group of VLBW preterm infants undergoing intensive care, to determine the overall prevalence of gastro-oesophageal reflux, the association with postconceptional age and with lower oesophageal sphincter pressure, and the effects of position, feeds, and nursing care. In addition, we studied the association between gastro-oesophageal reflux and apnoea in a separate group of VLBW infants with frequent attacks of apnoea.

## Subjects and methods

### VLBW PRETERM INFANTS RECEIVING INTENSIVE CARE

Fifty seven studies were carried out on 35 preterm infants in the regional neonatal referral unit at Birmingham Maternity Hospital. Infants included were consecutive patients weighing less than 1500 g who met the inclusion criteria, and for whom informed parental consent could be obtained. Exclusion criteria included the presence of symptoms suggestive of gastro-oesophageal reflux such as vomiting or the aspiration of milk from the oropharynx. Infants were also excluded if they had evidence of other gastrointestinal disease, if they were severely ill, or if they had severe recurrent apnoea. Infants with mild apnoea who were having less than four episodes a day, and who did not require treatment were included (n=25); in 10 infants apnoeic episodes had not been noted before the study.

Median (range) birth weight was 1040 (720–1470) g; gestation 28 (25–33) weeks; and postnatal age 2 (0–7) weeks. Gestation was determined from antenatal history and the Dubowitz assessment.[5] All but two infants were receiving milk feeds (median volume 132 ml/kg/day) reflecting a policy of early introduction of enteral feeds wherever possible. Among the infants studied there was a broad range of diagnoses typical of a neonatal intensive care unit: 31 studies were carried out on infants receiving supplementary oxygen, and six on infants receiving assisted ventilation. Four infants has hyaline membrane disease, nine infants has chest infections, five had bronchopulmonary dysplasia, three were being treated for septicaemia, and eight were small for gestational age.

### INFANTS WITH FREQUENT ATTACKS OF APNOEA

In the second investigation only infants with frequent apnoea were studied. Apnoea was defined as an episode of absent chest movement of greater than 20 seconds with or without cyanosis, or of bradycardia with cyanosis. Recovery followed stimulation with or without the administration of oxygen. 'Frequent apnoea' was defined as 12 or more such episodes in 24 hours.

Three subgroups were studied:

The first subgroup comprised six infants with frequent untreated attacks of apnoea. Three of these were studied before treatment was started. In the other three, frequent attacks of apnoea were associated with periventricular leucomalacia (n=2) or upper airways obstruction (n=1), and treatment with xanthine derivatives was considered inappropriate.

The second subgroup comprised eight infants with xanthine sensitive apnoea who had previously had frequent attacks of apnoea but, at the time of the study, were having less than three episodes a day during successful treatment with a xanthine. Xanthines used were theophylline (loading dose 7·5 mg/kg, and maintenance dose 3 mg/kg/day, which was adjusted to maintain serum concentrations at 13–20 mg/l), and caffeine (loading dose 50 mg/kg, and maintenance dose 12 mg/kg/day, which was adjusted to maintain serum concentrations at 28–40 mg/l).

The third subgroup comprised 13 infants with xanthine resistant apnoea. These infants had frequent attacks of apnoea that were unaffected by the administration of a xanthine and after full investigation had no evidence of central nervous system disorder, airways obstruction, or other primary cause for the apnoea.

The data from the infants with frequent attacks of apnoea were compared with those from the VLBW preterm infants receiving intensive care who had had no apnoeic episodes at all (n=10). None of the subgroups among the apnoeic babies differed significantly with respect to birth weight, gestation, age, or feeding. As in the VLBW preterm infants, none of them had clinical features of gastro-oesophageal reflux.

### MEASUREMENT OF GASTRO-OESOPHAGEAL REFLUX

Intraoesophageal pH was monitored continuously for 24 hours using an intraluminal pH probe. A simultaneous record of heart rate was made from the neonatal monitor (Hewlett-Packard, type 78801).

#### *pH probe*

A new 1 mm monocrystalline antimony electrode (Monocrystant—infant) was developed in conjunction with Synectics Medical. The antimony electrode produced a corrosion potential (−53 mV/pH) proportional to the surrounding pH relative to a reference electrode.[6] Although corrosion or oxidation of the surface of the crystal is minimised by cleavage of the crystal along a crystal plane,[6] careful calibration of the electrode before and after studies was essential. This was carried out using non-phosphate buffers (Synectics Medical) at pH 7·0 and 1·0. Calibration was considered satisfactory and data accepted if the pH electrode gave a stable reading between 6·9 and 7·1 for 10 minutes in a buffer with a pH of 7·0, and also after immersion in a solution with a pH of 1·0, showing a recovery to pH >6·7 in less than 15 s when reimmersed in a solution with a pH of 7.

No consistent drift was noted, and when stability was tested in a buffer with a pH of 7 for 24 hours the maximum deviation from the pH of 7 was 0·2.

Antimony electrodes age as the surface of the antimony crystal becomes slowly corroded. Calibration remained satisfactory for between 3 and 17 (mean 8·3) days of use.

#### *pH recording*

A karaya gum electrocardiograph electrode (Arbo pink H28) was used as a skin reference and produced stable contact with neonatal skin.

The potential generated by the pH electrode was amplified by a patient isolated amplifier (Ormed pH unit 4990, in preamplifier housing MT4PX-48) and recorded on a chart recorder (Philips PM 8216).

#### *Positioning the pH electrode*

The 1 mm pH electrode was bonded to a medical grade PVC nasogastric tube (umbilical arterial catheter, 3·5 Charrière, external diameter 1·2 mm) with a solvent welding solution (Vynol glue) such that the nasogastric tube extended 5 cm beyond the tip of the pH probe. The tube had a single end opening, and was attached to a previously described manometric system[7] continuously perfused at 3 ml/hour. This was used to determine the position of the high pressure zone of the lower oesophageal sphincter and the level of the diaphragm. The nasogastric tube was then advanced 3–4 cm below the diaphragm into the stomach, leaving the pH electrode in the lower oesophagus 1–2 cm above the sphincter. Radiography was not used. The manometric system was used at the end of each study to measure resting lower oesophageal sphincter pressure.[7]

### FEEDS AND NURSING CARE

During the study the infants were fed through nasogastric tubes using a standard feeding regimen[8] and no change was made in routine care. Timing of feeds, nursing care, and position changes were marked on the recordings using an event marker. Nursing care comprised chest physiotherapy, oropharyngeal or endotracheal suction, and nappy changing. Physiotherapy was performed by a nurse for a few minutes while the infant remained in the incubator. The procedure included turning the infant and was followed by oropharyngeal and endotracheal tube suction using a fine catheter. Whenever necessary the nappy was changed in the incubator and a clean nappy loosely applied. Infants were routinely nursed in three positions: prone, or right or left lateral.

### ANALYSIS OF DATA

Gastro-oesophageal reflux was defined as a fall in intraoesophageal pH to less than 4 for more than 15 seconds.[9] The following were recorded from the traces: the number of episodes in 24 hours; the number of episodes of more than five minutes duration in 24 hours; the longest single episode of reflux in minutes; and the reflux index, which was defined as the percentage of the observation period during which the pH was less than 4.

Table 1 *Incidence of gastro-oesophageal reflux in 57 studies of 35 VLBW preterm infants receiving intensive care*

| | *Mean (SEM)* |
|---|---|
| No of episodes/24 hours | 12·1 (2·1) |
| No of episodes lasting ≥5 min/24 hours | 3·2 (0·6) |
| Reflux index (%) | 4·5 (1·0) |
| Longest episode (min) | 17·1 (4·6) |

The effects of feeds and nursing care were determined by comparing gastro-oesophageal reflux in the 30 minute epoch preceding feeds or nursing care with the 30 minute epoch afterwards. The effect of position was evaluated by comparing the cumulative amount of reflux during four hour periods in each position.

Statistical analysis was by Student's *t* test. Values are expressed as mean (SEM) and, where comparisons are made, with standard error of the difference between the means (SE diff). The protocol was approved by the district research ethical committee, and informed consent obtained from the parents before each study.

## Results

### VLBW PRETERM INFANTS RECEIVING INTENSIVE CARE

*Incidence of gastro-oesophageal reflux (table 1)*

Despite the absence of clinical reflux, a mean of 12 episodes/24 hours was observed, although only three in each 24 hours lasted longer than five minutes. The mean reflux index was 4·5 (1·0)%, and 85% of recordings showed a reflux index of >1%.

The amount of reflux did not correlate with either resting lower oesophageal sphincter pressure (r=−0·04), or with postconceptional age (r=0·12).

*Effect of feeds, nursing care, and position (table 2)*

At rest infants had little reflux (reflux index 1·8 (0·62)%), and there was a moderate, but not significant, increase after feeds (reflux index 3·8 (1·01)%, SE diff 1·2).

Physiotherapy and suction were associated with a pronounced increase in the amount of reflux (reflux index 16·4 (2·97)% SE diff 3·5, p<0·01). Nursing care was also associated with significant increases in the number of episodes (SE diff 0·23, p<0·01), and

Table 2 *Comparison of gastro-oesophageal reflux in 30 minute epochs before and after feeds, nursing care, and nappy change. Results are expressed mean (SEM)*

| | *No of episodes/30 minutes* | *No of episodes ≥5 minutes/ 30 minutes* | *Reflux index (%)* | *Longest episode (minutes)* |
|---|---|---|---|---|
| 30 minutes before feed or nursing care (n=481) | 0·20 (0·06) | 0·07 (0·03) | 1·8 (0·6) | 5·6 (2·0) |
| 30 minutes after feed (n=308) | 0·45 (0·16) | 0·10 (0·05) | 3·8 (1·0) | 7·2 (1·8) |
| 30 minutes after nursing care (n=158) | 1·4* (0·20) | 0·30* (0·06) | 16·4* (3·0) | 7·9 (1·3) |
| 30 minutes after nappy change by mother (n=13) | 1·7* (0·34) | 0·48* (0·19) | 27·0* (6·3) | 8·6 (2·1) |

*p<0·001 compared with value before feed or nursing care; n=number of 30 minute periods observed.

the number of episodes of longer than 5 minutes (SE diff 0·08 $p<0·01$). The event most likely to be associated with reflux was a nappy change performed by the infant's mother (reflux index 27·0 (6·3)%; SE diff 6·3, $p<0·001$) (table 2).

The prone and right lateral positions were associated with similar amounts of gastro-oesophageal reflux (reflux index 3·9 (1·2)%, and 3·5 (1·65)%, respectively; SE diff 2·0). There was a trend towards increased reflux in the left lateral position (reflux index 7·3 (2·8)%; SE diff 2·9), but this was not significant.

### INFANTS WITH FREQUENT ATTACKS OF APNOEA

There was no significant difference between those patients with frequent attacks of apnoea (reflux index 3·1 (1·1)%, and the 10 VLBW preterm infants without apnoea (reflux index 2·4 (0·7)%, SE diff 1·3).These results did not, in fact, differ from the overall mean found for all the VLBW preterm infants (table 3).

Successful treatment of apnoea with a xanthine was associated with significant increase in both the reflux index (5·85 (1·6)%, SE diff 1·6, $p<0·05$) (table 3), and the mean longest epidose ($p<0·01$).

Table 3 *Reflux index in infants without apnoea, with frequent untreated attacks of apnoea, and with xanthine sensitive apnoea*

| | *Mean (SEM)* |
|---|---|
| No apnoea (n=10) | 2·4 (0·7) |
| Frequent untreated attacks of apnoea (n=6) | 3·1 (1·1) |
| Xanthine sensitive apnoea (n=8) | 5·9 (1·6)* |

*$p<0·05$ compared with group with no apnoea.

Thirteen VLBW infants with xanthine resistant apnoea were studied. These infants did not differ from any of the other infants with respect to birth weight, gestation, postconceptional age, or feeding. The mean reflux index (16·5 (4·1)%) was raised compared with that of the VLBW preterm infants (SE diff 3·1, $p<0·01$). Inspection of the data, however, showed that there were two distinct subgroups of patients: though there was no difference in the frequency or severity of the attacks of apnoea in these two subgroups, six of the 13 had a reflux index within the observed range for VLBW infants receiving intensive care, (2·7 (0·9)%, SE diff 2·3), whereas the remaining seven infants had severe gastro-oesophageal reflux. The mean reflux index of

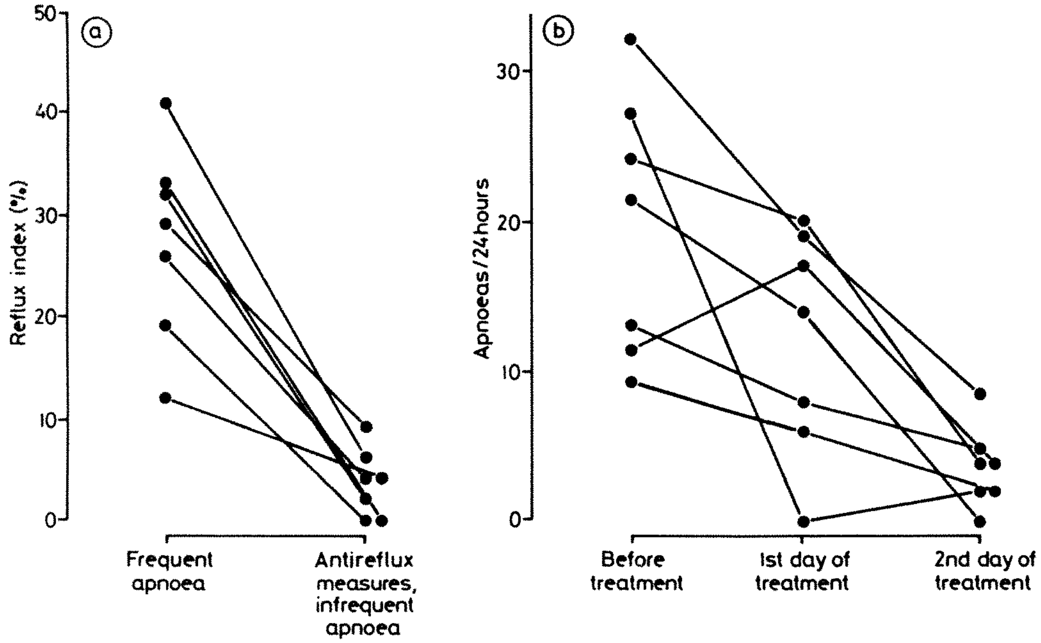

Figure *Xanthine resistant apnoea: intervention study. (a) Reflux indices in individual subjects before and after antireflux treatment ($p<0·001$); (b) Number of apnoea attacks/24 hours: before diagnosis of reflux, and on first and second days after starting antireflux treatment ($p<0·01$).*

Table 4 *Xanthine resistant apnoea: intervention study. Results are expressed as mean (SEM); n=7*

| | *No of episodes/24 hours* | *No of episodes ≥5 minutes/24 hours* | *Reflux index (%)* | *Longest episodes (minutes)* |
|---|---|---|---|---|
| Before treatment, severe apnoea | 48·9<br>(6·7) | 18·4<br>(3·2) | 27·4<br>(3·6) | 35·0<br>(4·1) |
| After treatment for gastro-oesophageal reflux, no apnoea | 10·9*<br>(4·1) | 2·9*<br>(1·1) | 3·6*<br>(1·2) | 24·0<br>(9·9) |

*p<0·01 compared with value before treatment.

these seven (27·4 (3·6)%, SE diff 2·7) was grossly raised (figure). Other indices of reflux were also much higher than in the other study groups (table 4). In these infants, comparison of the heart rate record with the oesophageal pH trace failed to show a temporal association between episodes of apnoea and gastro-oesophageal reflux.

XANTHINE RESISTANT APNOEA: INTERVENTION STUDY

Antireflux management was instituted in the seven infants with high reflux indices: patients were nursed prone and tilted 30° head up, and, in the four patients with reflux indexes of over 20%, feeds were thickened (Carobel, Cow and Gate: 0·3–0·6 g/100 ml suspension). Successful control of reflux was associated with a pronounced reduction in the frequency of apnoea attacks over a period of 12–48 hours after the introduction of antireflux management (figure); the mean (SEM) number of apnoeic episodes in 24 hours was 19·4 (3·3) before treatment, and fell on the first day of treatment to 12·0 (2·8) (SE diff 4·3), and on the second day of treatment to 3·6 (1·0), (SE diff 3·4, p<0·01). This clinical improvement was maintained when the xanthine treatment was withdrawn. pH studies were repeated between two and 11 days after the onset of antireflux measures, while infants were still receiving treatment. The mean reflux index had fallen from 27·4 (3·6)% to 3·6 (1·2)%, (SE diff 3·8, p<0·001), and there was also a highly significant reduction in the number of episodes and the number of episodes lasting longer than 5 minutes (SE diff 3·4, p<0·01); the reduction in the mean longest episode was not significant (table 4, figure).

Consent was obtained to study three of the seven infants with reflux again at between 38 and 43 weeks' postconceptional age (six to 11 weeks after the study after treatment). The studies were performed over 24 hours during temporary withdrawal of feed thickeners. Reflux indices in all three were still abnormal (mean reflux index 15·2 (1·2)%). All infants remained on feed thickeners until weaned.

## Discussion

We have shown that clinically undetectable gastro-oesophageal reflux is common among preterm infants. Reflux is increased by nursing procedures and by xanthines, and there is a strong association between apnoea and reflux in the small group of infants with xanthine resistant apnoea, who responded well to antireflux measures.

Of the various methods available, continuous intraoesophageal pH measurement is now well established as the single most sensitive method of monitoring gastro-oesophageal reflux.[10 11] Since the development of the 1 mm pH electrode, which permitted easy passage of the combined probe and nasogastric tube, it was possible to use this technique even in infants weighing under 1000 g. The technique is well suited to use in the intensive care unit, as the infants' routine care and feeding regimens need not be disturbed.

Gastro-oesophageal reflux is more common in asymptomatic, preterm infants than has previously been reported in infants born at full term,[11] or older children.[12 13] In our group of VLBW preterm infants receiving intensive care, however, there were no discernible symptoms associated with gastro-oesophageal reflux, nor did it change within the range of maturation studied.

We have previously shown that lower oesophageal sphincter pressure rises with increasing maturity,[7] and yet no correlation was found between gastro-oesophageal reflux and postconceptional age. In common with previous studies in adults we also failed to show a correlation between resting lower oesophageal sphincter pressure and gastro-oesophageal reflux.[14] It is possible, therefore, that inappropriate relaxation of the sphincter is the mechanism of reflux in these babies. We cannot, however, entirely rule out the possibility that the presence of a nasogastric tube promotes reflux.

We found only a small increase in reflux index after feeds above the low values seen at rest. Postprandial reflux is well recognised,[12] and the smallness of the increase seen here may be caused, at least in part, by the buffering of gastric acidity by the feed. In well, preterm infants on 120–240 ml/kg/day (taken as three hourly formula feeds) intragastric pH rises above pH 4 for up to 90 minutes after a feed.[15] In our study infants were fed smaller volumes as hourly bolus feeds. We have measured intragastric pH in eight such infants on 90 ml/kg/day, and found that buffering to over pH 4 occurred after 28% of feeds, and lasted up to 25 minutes. Clearly therefore, our observations may underestimate the importance of postprandial reflux.

There was, however, a strong temporal association between gastro-oesophageal reflux and nursing care. Though oropharyngeal or endotracheal suction might provoke gastro-oesophageal reflux through stimulation of the retropharynx, it was also associated with other nursing procedures. It was most pronounced after nappy changes performed by the infants' mothers, who presumably had less expertise than that of the nurses.

Though there was some increase in the reflux index and the number of episodes lasting longer than five minutes when the babies were nursed in the left lateral position, there is no evidence to recommend any change in the three positions used for routine care. The supine position was avoided because of its well recognised association with gastro-oesophageal reflux.[16]

The putative association between apnoea and gastro-oesophageal reflux remains contentious.[3 17] We found that among infants who had frequent attacks of apnoea all indices of reflux were marginally higher than in those infants who had no apnoea. This difference was not significant. In contrast, however, in those infants whose apnoea had been successfully treated with a xanthine, even though the frequency of attacks was reduced, significantly higher indices of reflux were observed than in non-apnoeic subjects. These observations are consistent with previous studies in which xanthines have been shown to increase gastro-oesophageal reflux in infancy[18] and to reduce lower oesophageal sphincter pressure in adults.[19]

Our data strongly support the hypothesis that in a subgroup of infants with apnoea, there is a close association with gastro-oesophageal reflux. Routine investigation of attacks of apnoea in seven infants showed no cause for the apnoea but, unlike infants with primary apnoea, these infants did not respond to xanthine derivatives. There was, however, a dramatic response to antireflux measures. Short term follow up of these infants suggests that they continue to reflux, but that (in common with most infants with gastro-oesophageal reflux) this tendency resolves with increasing age.

The mechanism by which reflux associated apnoea is mediated is unknown. Authors disagree about whether episodes of reflux and apnoea occur simultaneously.[3 17 20 21] In our study reflux and apnoea were not simultaneous. We also noted that following the introduction of treatment for gastro-oesophageal reflux, apnoea attacks did not stop until 12–48 hours later (figure). This suggests that a vagally mediated reflex secondary to stimulation of laryngeal chemoreceptors by regurgitated milk[22 23] is unlikely to be important here. It is possible, however, that apnoea associated with severe gastro-oesophageal reflux is mediated through a vagovagal reflex secondary to oesophagitis and abnormal oesophageal motility,[24 25] both of which are recognised complications of reflux.[3 26 27]

What are the implications of these findings for the management of xanthine resistant apnoea in preterm infants receiving intensive care? The performance of reflux studies in VLBW infants is, and will probably remain, essentially a research procedure. A pragmatic approach may therefore be adopted. On finding a preterm infant with xanthine resistant apnoea in the absence of other demonstrable aetiology a trial of antireflux treatment may be started. If successful in controlling apnoea, xanthines (which may aggravate reflux) could then be withdrawn.

In conclusion, we have found that gastro-oesophageal reflux is common and that, even when severe, it may not be immediately apparent clinically. The evidence for the association with nursing care may have implications that merit discussion with nursing colleagues. Reflux was not generally increased in infants with apnoea, but our data suggest a causative association in a subgroup of infants with xanthine resistant apnoea. Clearly the role of reflux in the aetiology of neonatal apnoea deserves further evaluation, and highlights the importance of studies of gastro-oesophageal reflux in this age group.

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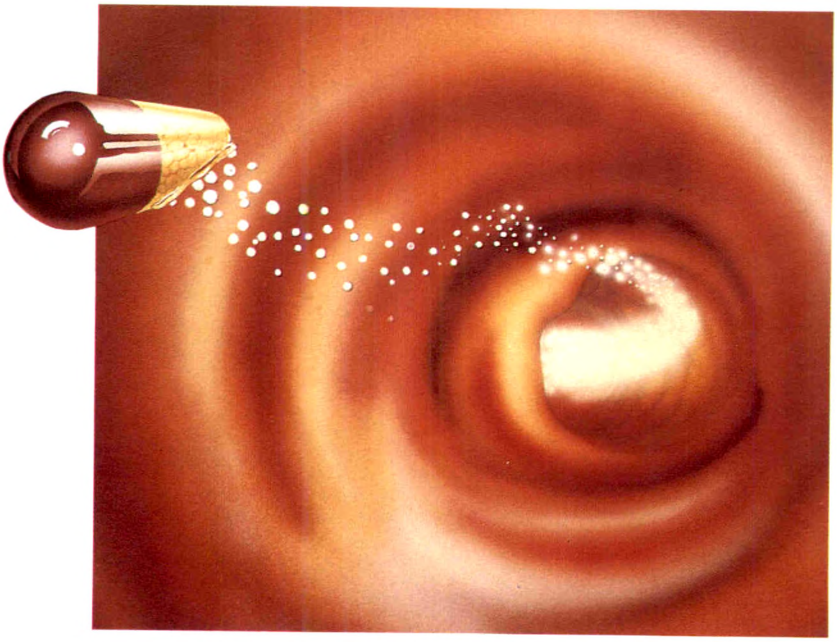

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# Early diagnosis and secondary prevention of Duchenne muscular dystrophy

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SUMMARY A total of 33 young boys (mean age 3·4 years) with Duchenne muscular dystrophy and 21 normal controls (mean age 3·5 years) were assessed using the Griffiths's mental development scales and the Reynell language scales. The boys with Duchenne muscular dystrophy were significantly developmentally delayed when compared with the control group. The developmental delay was most pronounced in locomotor function and language. There was no significant difference in social class distribution. Early diagnosis of Duchenne muscular dystrophy is of vital importance if secondary cases within families are to be prevented. While diagnosis is still unacceptably late in most cases, it can be improved if all boys with this pattern of developmental delay are screened for Duchenne muscular dystrophy by measurement of creatine kinase activity.

Recent advances in the understanding of the molecular genetics of Duchenne muscular dystrophy have led to improvements in the determination of female carrier status and to the provision of reliable antenatal diagnosis for most pregnancies at high risk.[1] These advances highlight the importance of early diagnosis of Duchenne muscular dystrophy. Prevention of secondary cases within a kindred could now be achieved if early diagnosis was improved and genetic counselling offered. Early diagnosis is important for other reasons: it avoids the frustration for the parents of late diagnosis when symptoms have been ignored or misinterpreted, it allows for early comprehensive assessment and management, and has been shown to be wanted by parents.[2]

There are no obvious clinical signs of Duchenne muscular dystrophy in affected young boys. There are, also, no studies of large samples of young boys with Duchenne muscular dystrophy. We aim to show that by studying the early development of young boys with Duchenne muscular dystrophy a pattern of aberrant development can be demonstrated, which is helpful in directing attention to the possibility of this disease.

## Subjects and methods

We studied 33 young boys with Duchenne muscular dystrophy from 31 families. The average age on entry to the study was 3·4 years (range 0·8 to 6·4). Nineteen were from Wales and 14 were ascertained from various centres in England through paediatric and medical genetic units. They formed a heterogeneous group. Twelve were diagnosed in the asymptomatic phase because of a family history, 12 presented with developmental delay, and nine presented with locomotor problems. All had very high creatine kinase activities. Twenty four had the diagnosis confirmed by a muscle biopsy specimen and the remaining nine had a positive family history with an affected relative who had had a confirmatory muscle biopsy. In none of the families was the pattern of disease suggestive of Becker muscular dystrophy. A control group of 21 normal boys, matched for age, were recruited from the Cardiff birth register.

Formal developmental assessments were carried out on both groups of boys using the Griffiths's mental development scales[3] and the Reynell language scales.[4] All assessments were carried out by one observer (RAS) in the subject's home; this was deemed to be the best environment to obtain maximum cooperation.

The Griffiths's mental development scales are a widely used set of scales standardised on normal British children. They assess six main areas of development: locomotor, personal-social, hearing-speech, eye-hand coordination, performance, and practical reasoning. The practical reasoning scale starts at the third year. Scores are given as a mental age in months, based on items scored, which when divided by the actual age gives a quotient for each subscale. The overall general quotient is the mean of the subquotients. The current mean quotients on the Griffiths's scales for normal children are 110; this reflects the out of date standardisation of the Griffiths's scales.

The Reynell language scales are standardised on normal British children and assess verbal comprehension and expressive language. The scores are given in terms of equivalent age levels and standard scores. This scale has been recently restandardised.

Statistical analysis was performed using the Student's *t* test and $\chi^2$ test.

## Results

The overall mean developmental quotients and mean subscale quotients achieved by both groups of boys on the Griffiths's scales are presented in table 1. The scores achieved by the boys with Duchenne muscular dystrophy were significantly lower than the control group on all subscales with a more noticeable discrepancy on the locomotor and hearing-speech subscales. Seventeen (52%) boys with Duchenne muscular dystrophy scored below 80 on overall Griffiths's quotient, 28 (85%) scored below 80 on the locomotor subscale, and 20 (61%) scored below 80 on the hearing-speech subscale. Only 18 boys with Duchenne muscular dystrophy scored items on the practical reasoning scale, which explains the larger standard deviation.

The mean scores of the subgroups of the group with Duchenne muscular dystrophy, based on mode of presentation, are presented in table 2. The pattern of subscale scores was similar for all three groups. The group diagnosed in the asymptomatic phase, because of a positive family history, had the lowest mean age and still show developmental delay. The group presenting later, with locomotor problems, had a higher mean age and the lowest locomotor score. The group presenting with developmental delay had the lowest mean language score.

Table 1 *Griffiths's subscales mean (SD) quotients*

| *Subscale* | *Boys with Duchenne muscular dystrophy (n=33)* | *Controls (n=21)* | *t* |
|---|---|---|---|
| Locomotor | 65 (13) | 112 (9) | 15·5* |
| Personal-social | 81 (17) | 110 (16) | 6·4* |
| Hearing-speech | 77 (19) | 110 (16) | 6·9* |
| Eye-hand coordination | 82 (16) | 108 (12) | 6·9* |
| Performance | 88 (15) | 116 (18) | 5·9* |
| Practical reasoning | 86 (21)† | 112 (17) | 4·9* |
| General quotient | 79 (14) | 111 (12) | 8·6* |
| Age (years) | 3·4 (1·6) | 3·5 (1·5) | |

*p<0·001; †n=18.

Table 2 *Griffiths's subscales mean (SD) quotients for boys with Duchenne muscular dystrophy*

| *Subscale* | *Developmental delay (n=12)* | *Locomotor delay (n=9)* | *Positive family history (n=12)* |
|---|---|---|---|
| Locomotor | 62 | 58 | 77 |
| Personal-social | 75 | 82 | 85 |
| Hearing-speech | 70 | 82 | 81 |
| Eye-hand coordination | 78 | 84 | 87 |
| Performance | 83 | 90 | 92 |
| Practical reasoning | 85 (n=6) | 84 (n=5) | 92 |
| General quotient | 74 | 80 | 85 |
| Age (years) | 2·8 | 5·2 | 2·6 |

The mean equivalent age and mean standard scores for the Reynell language scales are given in table 3. The two youngest boys age 10 months and 1 year 2 months were unable to perform any tasks on the Reynell scales. There is a highly significant difference between the standardised scores of the Duchenne muscular dystrophy group and the control group for both the verbal comprehension scale A and the expressive language scale. The control group had mean standard scores close to zero reflecting the more up to date standardisation of this scale.

Table 4 shows that there was no significant difference in social class distribution between the subgroups of boys with Duchenne muscular dystrophy or between the group with Duchenne muscular dystrophy as a whole and the control group.

Table 3 *Reynell language scales mean scores. The standard scores are given as SD*

| *Scale* | *Boys with Duchenne muscular dystrophy (n=31)* | *Controls (n=21)* | *t* |
|---|---|---|---|
| Verbal comprehension A equivalent age (years) | 2·6 | 3·7 | |
| Verbal comprehension A standard score | −1·53 | 0·16 | 6·5* |
| Expressive language equivalent age (years) | 2·45 | 3·3 | |
| Expressive language standard score | −1·74 | −0·38 | 5·5* |
| Age (years) | 3·6 | 3·5 | |

*p<0·001.

Table 4 *Social class distribution*

| *Social class* | *Subgroups for Duchenne muscular dystrophy (presentation)* | | | *Total boys with Duchenne muscular dystrophy* | *Controls* |
|---|---|---|---|---|---|
| | *Developmental delay* | *Locomotor delay* | *Positive family history* | | |
| 1 | 2 | 0 | 0 | 2 | 2 |
| 2 | 3 | 2 | 0 | 5 | 7 |
| 3 manual | 4 | 2 | 4 | 10 | 6 |
| 3 non-manual | | | 1 | 1 | 0 |
| 4 | 1 | 1 | 2 | 4 | 1 |
| 5 | 1 | 0 | 1 | 2 | 0 |
| Unemployed | 1 | 4 | 4 | 9 | 5 |
| Total | 12 | 9 | 12 | 33 | 21 |

For difference between Duchenne muscular dystrophy and controls $0{\cdot}5>p>0{\cdot}10$.

## Discussion

Locomotor delay and delay in language development have previously been reported.[5 6] Most information on early development in Duchenne muscular dystrophy, however, has been obtained retrospectively. The existence of early global developmental delay and the extent of delay in language development has not previously been reported. The Griffiths's and Reynell scales are often used by paediatricians in their initial assessment of children with developmental delay. Recognition of the pattern of developmental delay, which is shown in the present study, even in the youngest boys could lead to earlier diagnosis and improve secondary prevention rates.

The differences between the two groups of boys is too great to be explained by differences in social class or child rearing practices. Only one boy in the group with Duchenne muscular dystrophy and none in the control group had failed the routine hearing tests.

Despite efforts to encourage early diagnosis,[7–10] the detection of new cases of Duchenne muscular dystrophy remains unsatisfactorily late in most cases. Between 1970 and 1979, 43 boys were born in Wales who were later found to have Duchenne muscular dystrophy. During this period near complete ascertainment has been achieved. A population incidence for this period has been calculated to be 1/4400 based on estimated figures for boys born during this period and living to the age of 5 years. This figure is similar to other calculated population incidences.[11]

Accurate ages of diagnosis have been obtained from the clinical notes for 36 (84%) of these 43 cases. The mean age at diagnosis for these 36 boys is 4·9 years. This group can be subdivided into 25 first cases and 11 familial cases. The mean ages at diagnosis for these two groups is 5·2 years and 4·3 years respectively, suggesting that even a positive family history does not necessarily decrease age at diagnosis. Ages at diagnosis of various cohorts of boys with Duchenne muscular dystrophy have been determined to be 5·8 years,[8] 5·7 years,[8] and 4·7 years.[9] Thus late diagnosis remains a problem in Duchenne muscular dystrophy.

Secondary prevention is the main advantage of early diagnosis. Estimates for the number of theoretically preventable cases by neonatal screening vary. Thirteen per cent of 122 cases ascertained in the north east of England,[8] 10–12% in a cohort of patients in the Midlands,[8] and 8·3% of secondary cases could be prevented by neonatal screening for affected boys purely on theoretical grounds.[12] In the series of 43 patients born between 1970 and 1979 in Wales there were 28 (65%) isolated cases and 15 (35%) had more than one case per family. Five of the 43 cases (12%) could have been prevented by the earlier diagnosis of an affected sibling or cousin.

There are three main strategies available to improve early diagnosis: neonatal screening of all male births; screening of selected infant populations, and reliance on clinical diagnosis. Although newborn screening is certainly feasible,[13–15] in the absence of effective treatment for Duchenne muscular dystrophy it has not found favour in Britain. A screening programme involving testing boys for creatine kinase activity at the routine 6 week infant check up exists in West Germany.[16] The programme is voluntary, however, and the uptake has been low (14%). Based on retrospective data that showed that 50% of boys with Duchenne muscular dystrophy are not walking at 18 months, Gardner-Medwin proposed that those boys not walking at this age be tested for creatine kinase activity and this could be used as the basis for a screening programme.[8]

At present a population screening programme based on testing boys for creatine kinase activity who are unable to walk four independent steps at 18 months (when they have their routine developmental assessment by a health visitor) is being conducted in Wales, but it is too early to draw conclusions on its effectiveness.

We conclude that early diagnosis could be improved, even without population screening, if all boys with unexplained overall developmental delay, but with more noticeable delay in locomotor and language abilities, are systematically tested for Duchenne muscular dystrophy by measuring their serum creatine kinase activity.

We would like to thank the Muscular Dystrophy Group of Great Britain and Northern Ireland and all the consultants who provided patients for the study.

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# ADVANCE NOTIFICATION OF MEETING

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## No. 10—Perspectives in Paediatric Nutrition

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**Topics to include:**

| | |
|---|---|
| Infant Growth and Later Death Risk from Cardiovascular and Respiratory Disease | — Professor D Barker, Southampton |
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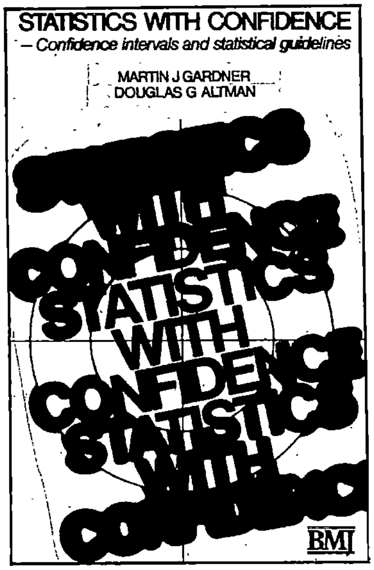
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# Respiratory control in infants at increased risk for sudden infant death syndrome

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SUMMARY There is much debate relating to possible abnormalities in respiratory control mechanisms in infants considered at increased risk for sudden infant death syndrome (SIDS). The $P_{0 \cdot 1}$ occlusion technique was used to assess the central respiratory response to hyperoxic hypercapnia during quiet sleep in 21 normal infants, 13 siblings of SIDS victims, and 17 infants with apparent life threatening events. The slope of $P_{0 \cdot 1}$ plotted against carbon dioxide concentration increased exponentially with age, independent of body weight in each group. Birth weight has a significant effect on slope with a lower weight predisposing to a lower slope. Siblings as a group had a significantly lower slope at any given age than normal infants, whereas the infants who had had apparent life threatening events were not significantly different from the controls. As intragroup variation in both siblings and control groups greatly exceeded the significant intergroup differences observed, the technique cannot identify individual infants as belonging to one or other group.

Considerable interest has been shown in respiratory control mechanisms in infants thought to be at increased risk for sudden infant death syndrome (SIDS). Shannon and Kelly reported resting alveolar hypoventilation and a reduced ventilatory response to hypercapnia in infants who had experienced an apparent life threatening event.[1] Others have failed to confirm these findings,[2-5] while Haddad *et al* have reported an increased ventilatory response to hypercapnia in infants experiencing apparent life threatening events when compared with controls.[6] These conflicting results may be due to a number of factors including varying criteria for infant selection, the suitability of comparison groups, differences in the methods used to assess the responsiveness of the respiratory system, and finally the wide variation in response to hypercapnia among normal infants.[7] The risk of SIDS in such infants has been shown to be slightly increased, particularly in those who 'required' resuscitation.[8]

Investigations of siblings of SIDS have failed to identify any abnormality in the ventilatory responses to hypercapnia.[2 4 5] Studies in this group of infants, however, produce conflicting results with regard to subsequent risk. Petersen *et al* concluded that there is no significant increase in risk of SIDS once correction has been made for maternal age and the birth order of the infant.[9] In contrast, Beal and Blundell found that risk is significantly increased in such cases, possibly up to fivefold, when compared with the general population.[10] This represents a risk for any individual sibling of about one in a 100.

Minute ventilation is the usual measure of the output of the respiratory system, but has the limitation that it depends on the mechanical properties of the respiratory system which may be impaired in the presence of disease. An alternative measure, the $P_{0 \cdot 1}$ occlusion pressure, is independent of the flow resistance and compliance of the respiratory system in healthy individuals as during the manoeuvre there is no flow and only a very small change in lung volume, due to decompression.[11] If this occlusion technique is applied during hyperoxic hypercapnic rebreathing, a measure of central chemoreceptor responsiveness to hypercapnia can be obtained.[12] We have utilised this technique to assess the central respiratory response to hyperoxic hypercapnic stimulation in infants at 'increased' risk for SIDS and in normal controls.

## Subjects and methods

Fifty one infants were studied successfully during natural sleep: 21 normal controls, 13 siblings of victims of SIDS, and 17 infants who had had an apparent life threatening event (table 1). Attempts were made to study an additional 19 infants who did not settle sufficiently for the test to be performed. The 19 infants who failed to settle comprised eight normal controls, eight siblings of SIDS victims, and three infants suffering from apparent life threatening events (these infants were studied as inpatients with no real limit on the time available for testing). The infants who failed to settle were comparable clinically with those in whom studies were successful. Many appeared to be 'light sleepers' who were readily roused on being touched or handled.

The apparently normal healthy infants volunteered by their parents had no personal or family history of apnoea or respiratory problems or a family history of SIDS. All were growing and developing normally. The siblings were otherwise normal infants born to families that had experienced a previous infant death consistent with SIDS by history and postmortem examination. The remaining infants had all had an apparent life threatening event, for which either vigorous stimulation or mouth to mouth resuscitation had been applied before normal breathing was restarted. The description of episodes in these infants varied considerably. Ten of the 17 successfully studied were said to be cyanotic when found, 10 apnoeic, four pallid, and eight limp or floppy. Parents felt that their action had been life saving. Investigation had failed to show a convincing explanation for these events.[13]

Infants were studied in the evening after a normal feed. A questionnaire was completed with medical, social, and family details. Each infant was weighed and its length measured at the completion of the test. The studies were performed in a quiet darkened room with an environmental temperature of 20–23°C with the infants supine or on their sides. Chest movements were recorded by two symmetrically placed magnetometers and abdominal movements by a Graseby respiratory sensor placed lateral to the umbilicus. An electrocardiogram was recorded using disposable self adhesive electrodes (Z-100-A Medicotest) that were placed on the left and right sides of the chest anteriorly and on the abdomen. An electroencephalogram was recorded from two channels (B1/9 silver/silver chloride electrodes, Specialised Laboratory Equipment) placed sagitally in the frontal and parietal regions, and an electro-oculogram recorded from disposable self adhesive electrodes (C-50-S Medicotest) placed as diagonal pairs by the outer canthus of each eye. An electromyogram was recorded by self adhesive electrodes (C-50-S Medicotest) placed symmetrically beneath the chin overlying the digastric muscle.

These signals were recorded on a Mingograph 81 ink jet 8 channel recorder (Elema Schonander) with a paper speed of 5 mm/second. Sleep was staged, by an independent observer, using the criteria set out by Anders *et al*, as quiet, active, or indeterminate sleep.[14]

Hyperoxic hypercapnic stimulation was achieved using the rebreathing technique of Read.[12] Infants breathed a mixture of 5% carbon dioxide in 95% oxygen through an appropriate sized face mask (Rendell Baker size 1 or 2) from a closed circuit incorporating a Jaeger screen pneumotachograph (linear to 700 ml/second) connected to a one litre anaesthetic rebreathing bag. A shutter system separated the pneumotachograph and face mask from the rest of the circuit. Thirty of the tests were performed with an electromechanical solenoid shutter which, when triggered, would close at end expiration. (End expiration was detected when the flow signal reached zero flow.) The remaining 21 tests were performed using an electrically controlled shutter built into the inspiratory limb of a one way

Table 1 *Clinical details of infants studied*

| | *Normal controls* | *Siblings of SIDS victims* | *Infants with apparent life threatening event* |
|---|---|---|---|
| No of infants | 21 | 13 | 17 |
| Sex ratio (M/F) | 10/11 | 5/8 | 11/6 |
| Birth weight (SD) (g) | 3300 (360) | 3400 (530) | 3400 (480) |
| Gestational age (SD) (weeks) | 39·7 (0·86) | 40·1 (0·95) | 38·7 (0·48) |
| Weight at test (SD) (g) | 4900 (1290) | 5800 (980) | 5400 (1120) |
| Length at test (SD) (cm) | 56·7 (4·76) | 58·8 (3·71) | 59·5 (4·76) |
| Decimal age (years) | | | |
| Median | 0·14 | 0·20 | 0·19 |
| Range | (0·006–0·43) | (0·13–0·34) | (0·04–0·47) |

There were no significant differences between the three groups (p>0·05).

valve. When triggered this closed the inspiratory limb during expiration.

Both valves had resistance of less than 5 cm $H_2O$/l/second at tidal flow rates. No statistical differences were observed between the results obtained from the two systems, and the results were therefore combined.

The concentrations of carbon dioxide and oxygen in the rebreathing bag were recorded continuously by an infrared analyser (Datex CD102 Normocap) with oxygen electrode through which gas was withdrawn and returned to the bag at a constant rate of 50 ml/minute. The analyser was calibrated and its linearity was checked using concentrations of carbon dioxide up to 8% and thereafter a two point calibration was used on a daily basis.

Pressure generated at the mouth was recorded by a Validyne MP 45 pressure transducer (range ±56 cm $H_2O$) that had a frequency response linear to 10 Hz. The transducer was calibrated with a water manometer before each study.

Flow was recorded by a Furness Micromanometer (range±10 cm $H_2O$), calibrated using a specially constructed sine wave pump. The flow signal was integrated electronically to give tidal volume.

These signals were recorded on an ultraviolet recorder (Bryans Southern Instruments Ltd) at a paper speed of 50 or 100 mm/second and used for later analysis.

After the infant was switched into the rebreathing system a 20–30 second period was allowed for equilibration after which there was a linear rise in the carbon dioxide concentration in the bag. During this time the concentration of carbon dioxide in the bag was assumed to be in equilibrium with alveolar, arterial, and cerebral carbon dioxide concentrations. The period of rebreathing continued until the carbon dioxide reached 8% or the infant aroused. The concentration of oxygen in the bag never fell below 40%.

After initial equilibration and when carbon dioxide concentration was equivalent to 38 mm Hg the first brief occlusion was performed. Subsequent occlusions were performed at intervals of 20–30 seconds. Triggering ensured that airway occlusion occurred at the onset of inspiration and continued for a maximum of 200 milliseconds. Where possible rebreathing runs were repeated after a recovery period of at least five minutes.

### ANALYSIS

Flow, volume, and mouth pressure were recorded on the ultraviolet recorder and the record was analysed to determine the mouth pressure generated 0·1 second after the onset of inspiration against an occlusion (fig 1).

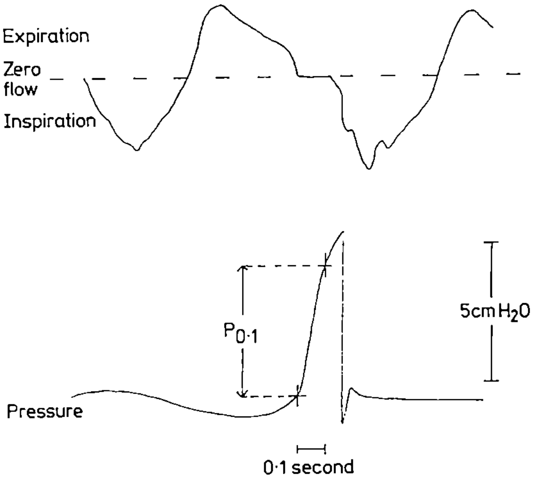

Fig 1 *Example of a recording: pressure 0·1 second (100 ms) after the onset of inspiration against an occlusion is the* $P_{0·1}$.

A plot of $P_{0·1}$ against end tidal carbon dioxide tension for each infant showed a linear relation over the range studied. Linear regression was therefore used to calculate the slope of the line (cm $H_2O$/mm Hg carbon dioxide) and to define the $P_{0·1}$ at 55 mm Hg carbon dioxide (cm $H_2O$) in the manner of previous authors. If more than one rebreathing run was obtained in a defined sleep state a common slope was calculated for each infant. Finally, a mean slope and mean $P_{0·1}$ at 55 mm Hg carbon dioxide was calculated for each group.

In 10 normal infants minute ventilation was calculated for the three breaths before the occlusion. A plot of minute ventilation against end tidal carbon dioxide tension for each infant showed a linear relationship over the range studied. The slope of this line defined the response to carbon dioxide (l/minute/kg/mm Hg carbon dioxide).

This simple analysis does not take into account the variability in quantity of data obtained from different infants. A minimum recording consisted of three points in a single rebreathing run whereas the maximum recording consisted of 36 data points from a total of six rebreathing runs. Fig 2 shows the variability in the data. Statistical weighting (proportional to the inverse of the variance) was used in the analysis to take account of this variability when combining results for different children.[15] This method was applied to data for each group and to those of the groups combined.

## Results

As shown by the non-parametric Kruskal-Wallis

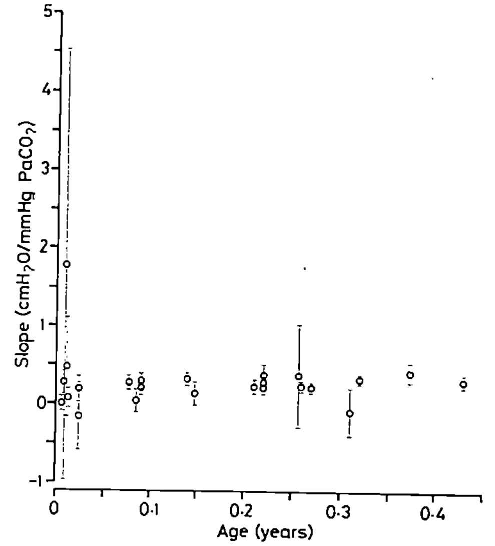

Fig 2 *Change in response to carbon dioxide with age in normal infants. Mean (2 SD) are shown.*

analysis, the three groups of infants were comparable with respect to their birth weight, gestational age, weight, length, and age (table 1). The normal infants were studied over an age range 3 days to 6 months, those with an apparent life threatening event from 1 week to 6 months, and siblings of SIDS victims from 6 weeks to 15 weeks.

Recordings were attempted both in quiet sleep and active sleep. Few data were obtained during active sleep and results presented here relate to quiet sleep. For each infant there was a linear relationship between mouth pressure ($P_{0\cdot1}$) and end tidal carbon dioxide concentration.

A wide range of slopes was observed within each group ranging from −0·13 cm $H_2O$/mm Hg carbon dioxide to +0·8 cm $H_2O$/mm Hg carbon dioxide. Seventeen of the 21 control infants had a slope between 0 and 0·4 cm $H_2O$/mm Hg carbon dioxide. Comparison of the values for slope and $P_{0\cdot1}$ at 55 mm Hg carbon dioxide among the three groups did not show statistical differences (table 2).

Further analysis of the data using statistical weighting showed an exponential increase in slope with age for all three groups of infants, as follows:

$\text{Slope}=0\cdot01102+0\cdot10354*\log_{10}(\text{age})+0\cdot9315*10^{-4}$ (weight, g), $p<0\cdot05$, for control infants;

$\text{Slope}=0\cdot01102+0\cdot10354*\log_{10}(\text{age})+0\cdot9315*10^{-4}$ (weight, g) $-0\cdot06521$, $p<0\cdot01$, for siblings;

$\text{Slope}=0\cdot01102+0\cdot10354*\log_{10}(\text{age})+0\cdot9315*10^{-4}$ (weight, g) $-0\cdot05338$, $p<0\cdot01$, for infants experiencing an apparent life threatening event.

Intergroup comparison shows that the siblings had a significantly lower value for slope at any given age than the normal infants ($p<0\cdot05$). The value for slope in the group with an apparent life threatening event did not differ significantly from that obtained in either the normal infants or siblings of SIDS victims (fig 3).

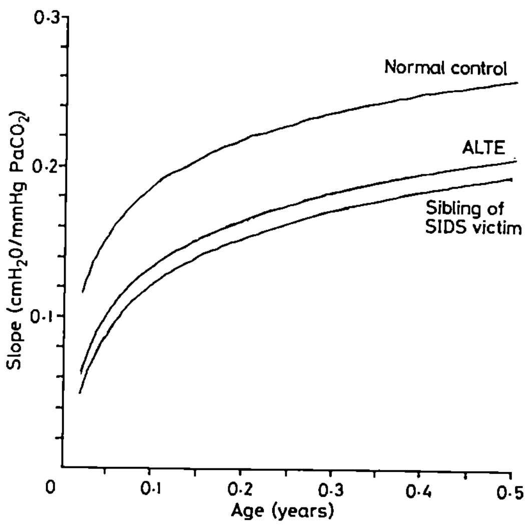

Fig 3 *The average slope at different ages for the three groups of infants standardised to a birth weight of 3000 g. ALTE=apparent life threatening event.*

Table 2 *Summary of the results obtained by simple linear regression*

| | *Normal controls* | *Siblings of SIDS victims* | *Infants with apparent life threatening events* |
|---|---|---|---|
| $P_{0\cdot1}$ slope (cm $H_2O$/mm Hg carbon dioxide) | | | |
| Median | 0·23 | 0·21 | 0·23 |
| Range | −0·13–0·47 | 0·12–0·80 | 0·12–0·46 |
| $P_{0\cdot1}$ at 55 mm Hg carbon dioxide (cm $H_2O$) | | | |
| Median (SD) | 7·12 (2·51) | 8·06 (2·81) | 8·11 (2·46) |

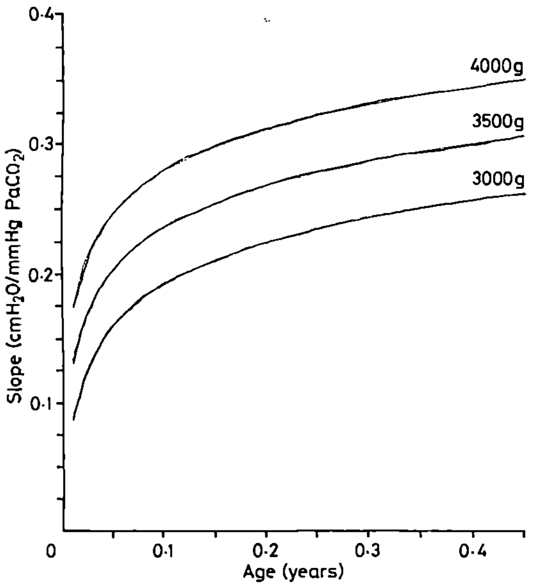

Fig 4 *Comparison of response to carbon dioxide in relation to birth weight.*

Using multiple regression to assess the influence of weight showed that there was no effect of weight at the time of testing on the age/slope association. Birth weight, on the other hand, exerted a significant effect with a smaller birth weight associated with a lower slope ($p<0{\cdot}02$) at any given age (fig 4).

In 10 normal infants we measured minute ventilation and $P_{0{\cdot}1}$ synchronously in an attempt to compare them as measures of output of the respiratory system. Both indices in these infants showed good correlation with carbon dioxide concentration ($P_{0{\cdot}1}$, $r=0{\cdot}913$ and $r=0{\cdot}954$ for minute ventilation) but that for minute ventilation was significantly stronger ($p<0{\cdot}05$).

## Discussion

Simple analysis of the data by linear regression shows a range of $P_{0{\cdot}1}$ slope and $P_{0{\cdot}1}$ at 55 mm Hg similar to previous studies in adults[11] and also similar to those of Cosgrove *et al* who reported a range of slope from 0·2–0·8 cm $H_2O$/mm Hg carbon dioxide in nine neonates.[16]

It is only when the variability in the data is taken into consideration that trends become apparent. The response to hypercapnia in infants increases with postnatal age in an exponential fashion. This increase is only 0·2 cm $H_2O$/mm Hg carbon dioxide over the first six months; this is much smaller than the variability between individual tests. This increase is not simply an effect of weight, which contrasts with the data of Avery *et al* for infants and adults showing that the ventilatory response to hypercapnia was related to body size rather than age.[7] It is consistent with the findings of Rigatto *et al* who showed a significant increase in ventilatory response in infants 27 days old compared with infants 2 days old.[17]

Our results show that the siblings of SIDS victims have, as a group, a statistically lower response to hypercapnia. Several studies have purported to show an abnormality in the response in the group with an apparent life threatening event[6 18 19] but we, in common with others, have not been able to confirm that.[2–5] Certain other groups of infants considered at increased risk for SIDS, for example, those with apnoea of infancy or those with mothers who are narcotic addicts, show a reduced response to hypercapnia.[20 21]

Although weight at time of testing was not a significant determinant of $P_{0{\cdot}1}$ birth weight did exert an effect in that infants of birth weight 3000 g had a significantly lower slope than those of birth weight 4000 g ($p<0{\cdot}02$).

The effect of the face mask upon the response to carbon dioxide cannot be determined in this study. It has been shown that application of a face mask to a newborn infant leads to an increase in tidal volume and a fall in respiratory frequency, with no significant changes in minute ventilation.[22] As it is impossible to measure $P_{0{\cdot}1}$ without the application of a face mask we cannot speculate on the influence of trigeminal stimulation on our measurements. The conditions of measurement, however, were the same for all three groups so that differences between them should not have been obscured by possible effects of the face mask.

Our data showing a large variation in response among babies as measured by $P_{0{\cdot}1}$ slopes (varying from $-0{\cdot}13$ to $+0{\cdot}8$ cm $H_2O$/mm Hg carbon dioxide) and ventilatory responses in 10 normal infants (varying from 0·014 to 0·052 l/minute/kg/mm Hg $PaCO_2$) and are in agreement with previous studies.[7] The significant differences we have shown between siblings and 'normal' infants is small when compared with the variability in the response within each group. Siblings of SIDS victims may therefore be a group in whom respiratory control mechanisms are slightly attenuated. This may simply be a factor in determining their subsequent risk rather than the sole cause of subsequent risk. If the latter were true the occasional infant might have a poor response and the others be within the normal range. The differences are not sufficient to allow identification of individual infants within a particular group.

The $P_{0\cdot1}$ is used as a measure of the neuromechanical output of the respiratory system but before the results can be assessed two potentially important factors must be taken into consideration.[23] The changes in inspired gas concentrations may influence the level of functional residual capacity and the contractile mechanism of the respiratory muscles. With regard to changes in functional residual capacity Garfinkel and Fitzgerald have shown that hyperoxia decreases it (by 12%) while hypercapnia and hypoxia both increase it (by 14–15%).[24] Changes in functional residual capacity even of this magnitude did not produce any alteration in $P_{0\cdot1}$.[24] We did not measure functional residual capacity but as we used a hyperoxic hypercapnic mixture we were unlikely to have produced a significant change in it. In vitro experiments by Fitzgerald *et al* have shown that during the brief duration of a rebreathing run the effects of carbon dioxide on muscle contractility are minimal.[23] We feel that the experimental constraints of our study are unlikely to have altered either functional residual capacity or the contractility of the respiratory muscles.

When comparing recordings of $P_{0\cdot1}$ and minute ventilation the latter correlated more strongly with carbon dioxide concentration, a finding in agreement with Lederer *et al.*[25] It should be noted that in all these infants lung function was assumed to be normal. The possibility remains that in infants with chest disorders the $P_{0\cdot1}$ may be a more representative measure of output than minute ventilation, which could be more affected by mechanical disturbances.

In conclusion, we have shown that the ventilatory response to hyperoxic hypercapnia, as measured by the $P_{0\cdot1}$ occlusion technique, increases in an exponential fashion with postnatal age. This increase is not dependent on weight but is influenced by birth weight. Siblings of SIDS victims have as a group a statistically lower than 'normal' response to hypercapnia whereas the group with an apparent life threatening event of infants does not differ significantly from 'normal'. Whether a 'poor' response to hypercapnia, irrespective of the clinical grouping we have applied, is a risk factor for SIDS is not known.

We should like to thank all the parents and infants involved for their time and patience. We are grateful to Dr P Swift for referring all siblings of SIDS for this study, and to the paediatricians at Leicester Royal Infirmary who referred cases for study. The work was supported by grants from the Foundation for the Study of Infant Deaths and Children Nationwide.

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# Long term survival and cure after childhood cancer

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SUMMARY Investigations of long term survival and evidence concerning cure among children surviving at least three years after most of the more common childhood cancers treated in Britain between 1960 and 1981 are reported. The results indicate striking improvements in survival beyond three years for many childhood tumours over this period. For most childhood tumours considered over 80% of those who had survived at least three years were alive 10 years later. Comparison of mortality observed among survivors with that expected for the general population showed evidence of cure among those who had survived at least three years after non-Hodgkin lymphomas and non-genetic retinoblastoma. Survivors of other tumours, with sufficient cases surviving beyond 10 years to examine excess mortality, rarely experienced an excess that exceeded one extra death per 100 survivors per year. Children who had survived at least 10 years after other embryonal tumours, soft tissue sarcomas, or osteosarcoma never experienced an excess mortality exceeding one extra death per 200 survivors per year.

Relatively little has been published on long term survival and evidence of cure after childhood malignant disease. Reasons for this are the rarity of the disease (an overall annual incidence of 1/10 000 below age 15 in Britain) and the fact that substantial improvements in short term survival have occurred only relatively recently for some of the more common diseases, including leukaemia. Large numbers of survivors are required for a satisfactory analysis of long term mortality and examination of evidence of associations between survival and possible explanatory factors like sex of survivor, or age and calendar year when diagnosed. Data are presented relating to almost all those who survived at least three years after childhood cancer and who had been treated in Britain between 1960 and 1981 inclusive. This provided sufficient numbers to enable a reliable analysis.

To obtain a greater understanding of curability we shall examine the specific causes of death in a further paper.

## Patients and methods

### ASCERTAINMENT OF CASES

The Childhood Cancer Research Group is routinely notified of tumours registered under the National Cancer Registration Scheme occurring in children aged under 15 and diagnosed in 1962 or later. This provides, within the limits of completeness of cancer registration, a population based series of childhood cancer cases occurring in Britain. Childhood cancer registration is estimated to include over 90% of incident cases.[1 2] In addition 2000 children who had survived at least three years, and who had been diagnosed between 1940 and 1961, were assembled from particular treatment centres where it was known that a complete (and therefore unbiased) list of cases was available.

Cases were included if diagnosed before 1982 and known to have survived at least three years. Follow up in relation to death was achieved by 'flagging' survivors at the National Health Service Central Registers, Southport and Edinburgh. Tumours were classified using a recently published scheme.[3 4]

To be included in the analysis histological verification of each diagnosis was required except that for: (a) *retinoblastoma* where 56 of the total of 874 diagnoses were based on observation at operation; (b) *central nervous system tumours* where 52 of the total of 2077 diagnoses were based on radiology, scans, or observation at operation; (c) *neuroblastoma* where five of the total of 431 diagnoses were based on biochemistry; and (d) *craniopharyngioma* where 23 of the total of 220 diagnoses were based on biochemistry or observation at operation. Of the 2450 diagnoses of leukaemia 87 were based on blood counts only.

### STATISTICAL METHODS

Survival curves and life tables were constructed using standard techniques decribed by Peto *et al*[5]; comparison of life tables was carried out using standard tests.[5] Mortality occurring during different periods of follow up after diagnosis was compared with that expected for the general population of Britain. Analysis was carried out for England and Wales, and separately for Scotland, and then the results combined for Britain. Observed and expected numbers of deaths were compared assuming that the observed number approximate a Poisson distribution with mean equal to the corresponding expected number. Tests of significance were based on exact Poisson methods.

## Results

There were 11 449 children who had survived at least three years who were eligible for analysis. Table 1 gives the number of these survivors after each tumour type with sufficient cases to examine variation in mortality with follow up and possible associations with explanatory factors. Large variations in long term survival prospects are shown in table 1. Over 60% of children who survived at least three years were alive 10 years later except those diagnosed with medulloblastoma or Ewing's tumour. For most tumours over 80% of these children were alive 10 years later.

The number of children who had survived at least three years available for analysis was affected both by incidence and survival. Although there was some evidence of changes in incidence of some tumour types during the study period,[6 7] much greater changes in survival have been observed.[7 8]

Variations in survival by sex of survivor, calendar year of diagnosis, and age at diagnosis are summarised in table 2. Table 3 summarises the results of comparing all causes of mortality observed among survivors with that expected from the general population. The observed and expected numbers of deaths were considered in several follow up intervals at varying times from diagnosis. For each tumour type, and for those follow up intervals with at least 100 survivors alive on entry, are given the numbers entering each follow up interval, the observed and expected numbers of deaths, the Poisson probability of the observed number of deaths given those expected, and finally a measure of the excess mortality among survivors.

Survivors were regarded as cured when the mortality of the group was statistically indistinguishable from that expected. There are known problems with this approach, as described below, but it does provide insight into the risk of dying compared with members of the general population of a similar age, sex, and date of birth. Using this as a formal definition of cure, then cure may be considered to have been reached when the Poisson one tailed p value exceeds some specified arbitrary value, 0·05 for example. We only assessed evidence of cure if the expected number of deaths beyond a specified follow up time was at least two.

Table 1 *Long term survival among children surviving at least three years*

| *Diagnosis* | *No of children surviving at least three years* | *(%) Still alive 10 years after survival to three years* | *Standard error (%)* |
|---|---|---|---|
| Acute lymphocytic leukaemia | 2335 | 63 | 1 |
| Hodgkin's disease | 948 | 74 | 2 |
| Non-Hodgkin's lymphomas | 507 | 85 | 2 |
| Neuroblastoma | 431 | 89 | 2 |
| Wilms' tumour | 930 | 94 | 1 |
| Retinoblastoma: | | | |
| Genetic | 399 | 93 | 1 |
| Non-genetic | 475 | 100 | 0 |
| Medulloblastoma | 480 | 56 | 2 |
| Ependymoma | 261 | 68 | 3 |
| Juvenile astrocytoma | 599 | 88 | 1 |
| Other astrocytomas | 737 | 82 | 1 |
| Osteosarcoma | 196 | 77 | 3 |
| Ewing's tumour | 191 | 57 | 4 |
| Fibrosarcoma | 221 | 90 | 2 |
| Rhabdomyosarcoma | 262 | 83 | 2 |
| Malignant testicular germ cell | 121 | 96 | 2 |
| Malignant ovarian germ cell | 113 | 94 | 2 |
| Other histological types | 2226 | | |

Table 2 *Variation in survival beyond three years by sex, calendar year, and age at diagnosis*

| *Diagnosis* | *Summary of statistically significant associations* | | | |
|---|---|---|---|---|
| | *Sex†* | *Calendar year at diagnosis‡ (before 1962, 1962–70, after 1970)* | *Age at diagnosis in years‡ (0–4, 5–9, 10–14)* | *Alternative grouping of age§ (years)* |
| Acute lymphocytic leukaemia | <0·0001 (F) | <0·0001‖ | * | |
| Hodgkin's disease | * | <0·0001‖ | 0·0026¶ | 0–10, 11–12, 13–14 |
| Non-Hodgkin lymphomas | * | * | * | 0–8, 9–11, 12–14 |
| Neuroblastoma | * | * | <0·0001¶ | 0, 1–2, 3–14 |
| Wilms' tumour | * | 0·0124‖ | 0·0004¶ | 0–1, 2–3, 4–14 |
| Retinoblastoma: | | | | |
| Genetic | * | * | * | 0, 1, 2–14 |
| Non-genetic | * | * | (0·0254)** | 0, 1, 2–14 |
| Medulloblastoma | * | 0·0012‖ | 0·0090¶ | |
| Ependymoma | 0·0274 (F) | 0·0364‖ | 0·0492‖ | |
| Juvenile astrocytoma | * | * | 0·0016‖ | |
| Other astrocytomas | * | 0·0012‖ | 0·0274‖ | |
| Osteosarcoma | * | * | * | 0–10, 11–12, 13–14 |
| Ewing's tumour | * | * | * | 0–8, 9–11, 12–14 |
| Fibrosarcoma | * | * | * | |
| Rhabdomyosarcoma | 0·0140 (M) | * | * | 0–2, 3–5, 6–14 |
| Malignant testicular germ cell | * | * | * | 0, 1, 2–14 |
| Malignant ovarian germ cell | * | 0·0336‖ | * | 0–10, 11–12, 13–14 |

*The relevant test was not significant at 0·05 level, two tailed test.
†(M) or (F) indicates sex with greater survival.
‡The p values result from a test for trend. For age at diagnosis there was no evidence of heterogeneity in the absence of a significant trend.
§The categories of subdivision for age at diagnosis were 0–4, 5–9, 10–14 except where indicated to the contrary in final column.
‖Survival increases with increasing calendar year of diagnosis or age at diagnosis.
¶Survival decreases with increasing age at diagnosis.
**p Value in parentheses is unreliably estimated and is ignored in the text.

Table 3 *Comparison of observed and expected mortality among children surviving at least three years*

| | *Years from diagnosis* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *3–4 (3–)** | | | | | *5–9 (or 5–)** | | |
| | *No of survivors* | *Deaths* | | *Poisson probability (p)†* | *Excess mortality‡* | *No of survivors* | *Deaths* | |
| | | *Observed (O)* | *Expected (E)* | | | | *Observed (O)* | *Expected (E)* |
| Acute lymphocytic leukaemic | 2335 | 464 | 1·4 | 0·000 | 11·2 | 1872 | 295 | 2·0 |
| Hodgkin's disease | 948 | 105 | 0·9 | 0·000 | 5·8 | 844 | 104 | 2·0 |
| Non-Hodgkin lymphomas | 507 | 36 | 0·5 | 0·000 | 3·6 | 471 | 33 | 1·1 |
| Neuroblastoma | 431 | 25 | 1·6 | 0·000 | 2·8 | 407 | 19 | 0·5 |
| Wilms' tumour | 930 | 32 | 1·7 | 0·000 | 1·7 | 896 | 17 | 1·2 |
| Retinoblastoma: | | | | | | | | |
| Genetic | 399 | 5 | 2·0 | 0·049 | 0·4 | 392 | 16 | 0·6 |
| Non-genetic | 475 | 0 | 1·0 | 1·000 | −0·1 | 472 | 0 | 0·7 |
| Medulloblastoma | 480 | 111 | 0·4 | 0·000 | 13·2 | 368 | 75 | 0·6 |
| Ependymoma | 261 | 43 | 0·2 | 0·000 | 9·0 | 219 | 28 | 0·4 |
| Juvenile astrocytoma | 599 | 21 | 0·5 | 0·000 | 1·7 | 576 | 30 | 1·0 |
| Other astrocytomas | 737 | 57 | 0·6 | 0·000 | 4·0 | 681 | 54 | 1·3 |
| Osteosarcoma | 196 | 29 | 0·2 | 0·000 | 7·9 | 167 | 14 | 0·4 |
| Ewing's tumour | 191 | 56 | 0·1 | 0·000 | 17·8 | 135 | 24 | 0·5 |
| Fibrosarcoma | 221 | 7 | 0·4 | 0·000 | 1·5 | 211 | 12 | 0·5 |
| Rhabdomyosarcoma | 262 | 26 | 0·3 | 0·000 | 5·3 | 234 | 14 | 0·3 |
| Malignant testicular germ cell | 121 | 3 | 0·3 | 0·006 | 1·1 | 117 | 1 | 0·8 |
| Malignant ovarian germ cell | 113 | 4 | 0·1 | 0·000 | 1·8 | 108 | 5 | 0·5 |

*The final follow up interval for each tumour type includes the whole period of risk beyond the entry year for that specific follow up
†A Poisson one tailed probability less than 0·0005 is reported as 0·000.

$$\ddagger \; \frac{(O-E)100}{\text{person years at risk}}$$

When cure was not identified in the above sense, the excess number of deaths (observed minus expected) divided by the person years at risk and multiplied by 100 provided a measure of excess mortality that was compared for different tumour types. This measure was interpreted as the extra number of deaths occurring among each 100 survivors per year.

The different tumour types were considered by taking account of both survival beyond three years and a comparison of observed and expected mortality from all causes.

### LEUKAEMIA

#### *Acute lymphocytic leukaemia*

Just over 60% of children who had survived at least three years were alive 10 years later (see table 1). Boys who had survived at least three years experienced lower subsequent survival than girls (fig 1). Although there was still an excess of deaths among survivors after 10 years' survival, it was only about one extra death per 100 survivors per year.

### LYMPHOMAS

Survival beyond three years was greater after non-Hodgkin lymphomas than after Hodgkin's disease (see table 1). Survival from three years, after Hodgkin's disease, was greater among children diagnosed more recently and when younger (see table 2 and fig 1). The excess mortality among children surviving at least 10 years from Hodgkin's disease was under one extra death per 100 survivors per year; 10 year survivors of non-Hodgkin lymphomas showed evidence of cure (see table 3).

### EMBRYONAL TUMOURS

#### *Neuroblastoma (including ganglioneuroblastoma)*

Survival beyond three years was substantially greater among children who had been diagnosed when younger (see table 2 and fig 2). Among those who had survived at least 10 years the excess mortality was less than one extra death per 200 survivors per year.

#### *Wilms' tumour*

Survival after three years was greater among children diagnosed more recently and among those diagnosed when younger (see table 2 and fig 2). The excess mortality among those who had survived at least five years was always less than one extra death per 200 survivors per year (see table 3).

#### *Retinoblastoma*

This tumour occurs in two forms: 'genetic' defined here as either bilateral disease or unilateral with another affected family member; 'non-genetic' is defined as unilateral with no known family history of the disease. Fig 2 includes a comparison of survival

|  |  | *10–19 (or 10–)** |  |  |  |  | *20–* |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Poisson probability (p)†* | *Excess mortality‡* | *No of survivors* | *Deaths* |  | *Poisson probability (p)†* | *Excess mortality‡* | *No of survivors* | *Deaths* |  | *Poisson probability (p)†* | *Excess mortality‡* |
|  |  |  | *Observed (O)* | *Expected (E)* |  |  |  | *Observed (O)* | *Expected (E)* |  |  |
| 0.000 | 4·6 | 801 | 29 | 1·2 | 0·000 | 1·1 |  |  |  |  |  |
| 0·000 | 3·2 | 479 | 25 | 2·1 | 0·000 | 0·8 | 133 | 6 | 1·1 | 0·001 | 0·6 |
| 0·000 | 1·7 | 291 | 2 | 1·5 | 0·430 | 0·0 | 127 | 1 | 1·1 | 0·675 | 0·0 |
| 0·000 | 1·1 | 292 | 9 | 1·0 | 0·000 | 0·4 | 151 | 4 | 0·6 | 0·003 | 0·4 |
| 0·000 | 0·4 | 633 | 9 | 2·0 | 0·000 | 0·2 | 220 | 7 | 1·1 | 0·000 | 0·4 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 0·000 | 0·9 | 324 | 15 | 1·2 | 0·000 | 0·5 | 188 | 4 | 1·2 | 0·037 | 0·2 |
| 1·000 | 0·0 | 403 | 3 | 1·5 | 0·190 | 0·0 | 190 | 1 | 1·6 | 0·790 | 0·0 |
| 0·000 | 5·6 | 197 | 21 | 1·3 | 0·000 | 1·1 |  |  |  |  |  |
| 0·000 | 3·0 | 151 | 18 | 0·9 | 0·000 | 1·4 |  |  |  |  |  |
| 0·000 | 1·2 | 379 | 26 | 1·5 | 0·000 | 1·0 | 135 | 1 | 0·7 | 0·495 | 0·0 |
| 0·000 | 1·8 | 498 | 35 | 2·1 | 0·000 | 0·9 | 230 | 13 | 1·5 | 0·000 | 0·8 |
| 0·000 | 2·1 | 103 | 5 | 0·8 | 0·001 | 0·4 |  |  |  |  |  |
| 0·000 | 2·5 |  |  |  |  |  |  |  |  |  |  |
| 0·000 | 1·2 | 184 | 4 | 1·0 | 0·018 | 0·2 | 117 | 2 | 0·7 | 0·158 | 0·2 |
| 0·000 | 1·5 | 126 | 3 | 0·6 | 0·022 | 0·3 |  |  |  |  |  |
| 0·551 | 0·0 |  |  |  |  |  |  |  |  |  |  |
| 0·000 | 0·4 |  |  |  |  |  |  |  |  |  |  |

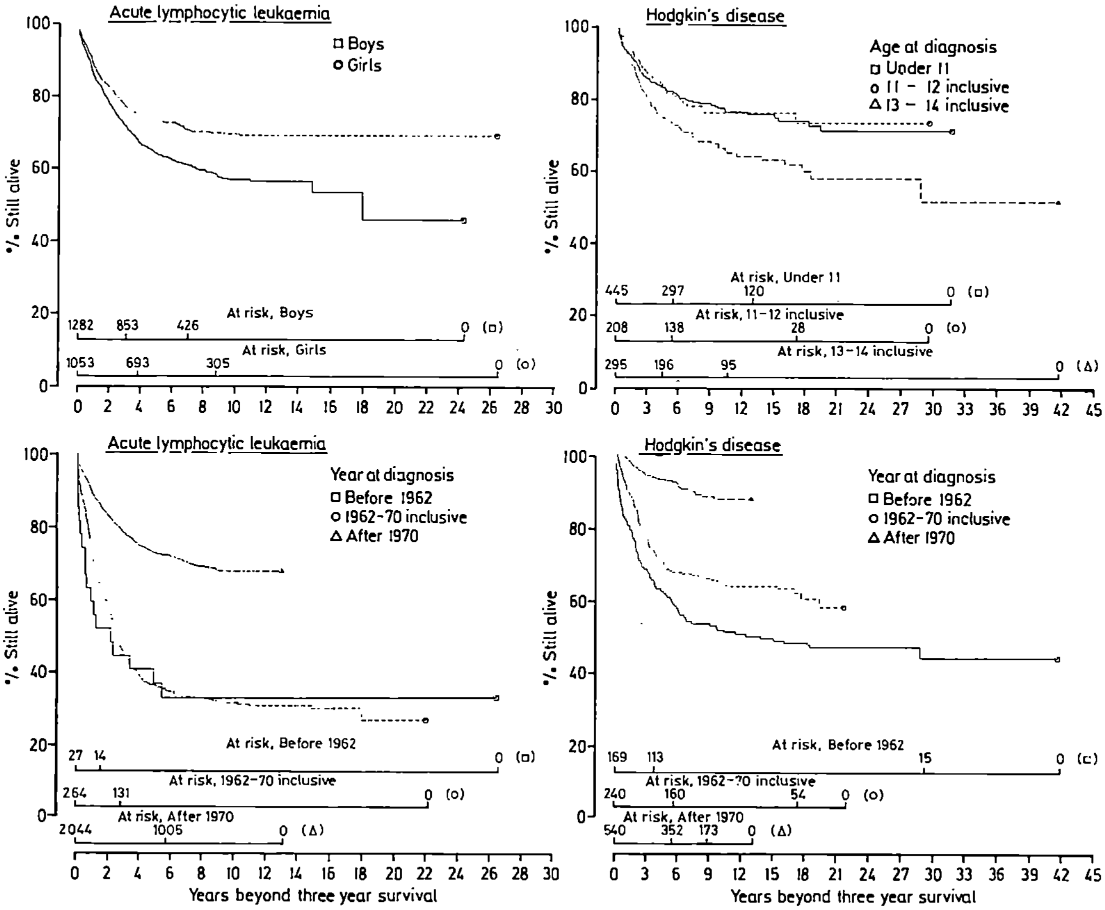


Fig 1 *Long term survival after acute lymphocytic leukaemia and Hodgkin's disease.*

subsequent to three years after genetic and nongenetic retinoblastoma. Those who had survived at least three years after retinoblastoma showed evidence of cure, but there was evidence of continuing excess mortality among survivors of genetic retinoblastoma.

### TUMOURS OF THE CENTRAL NERVOUS SYSTEM

Survival subsequent to three years improved among those diagnosed more recently with medulloblastoma, ependymoma, and other astrocytomas. Survival from three years was also greater among those diagnosed when older with ependymoma, juvenile astrocytoma, and other astrocytomas, in contrast with greater survival for those diagnosed when younger with medulloblastoma (see table 2 and fig 3).

The excess mortality after medulloblastoma decreased from 13 extra deaths per 100 survivors per year, at three and four years from diagnosis, to around one extra death beyond 10 years. The excess mortality among those who survived at least three years after juvenile astrocytoma was always less than two extra deaths per 100 survivors per year.

### MALIGNANT BONE TUMOURS

#### *Osteosarcoma*

The excess mortality among survivors decreased from about eight extra deaths per 100 survivors per year among those who had survived at least three or four years, to approximately one extra death per 200 survivors per year among those surviving at least 10 years.

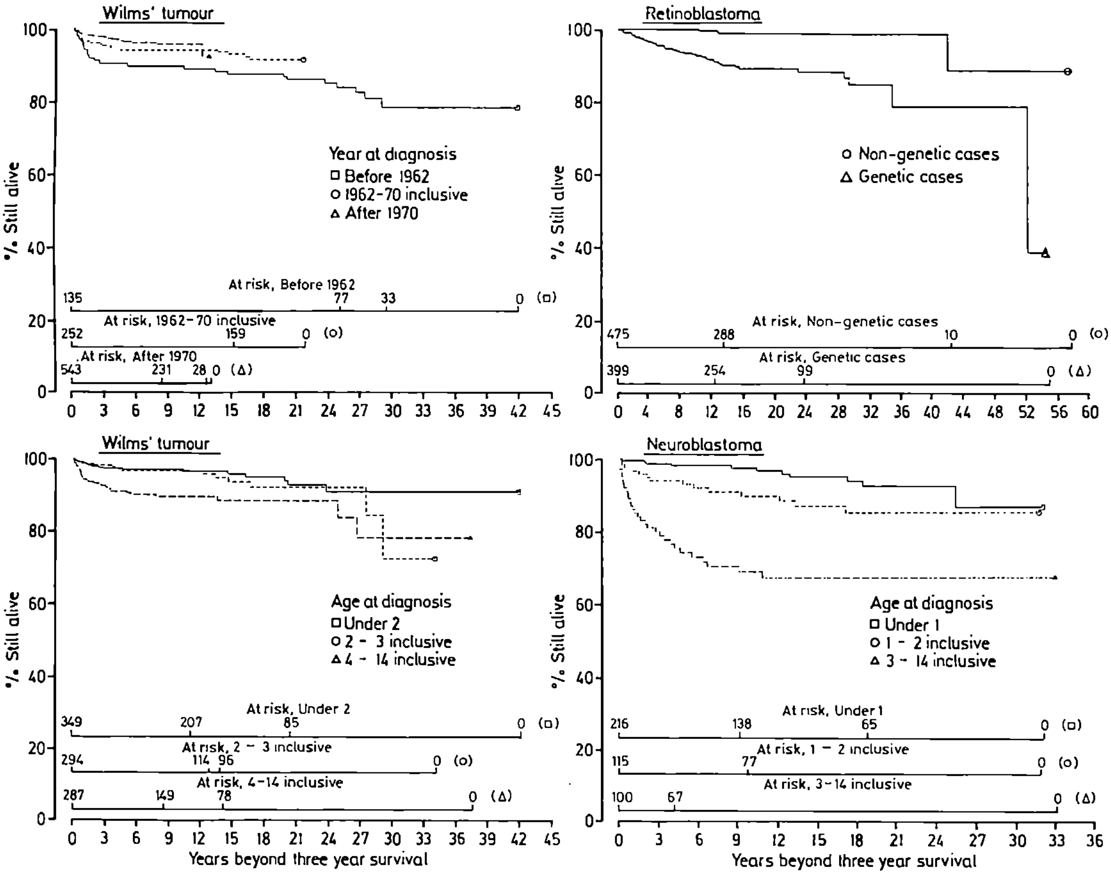


Fig 2 *Long term survival after Wilms' tumour, retinoblastoma, and neuroblastoma.*

### *Ewing's tumour*

The excess mortality among survivors was high at three and four years from diagnosis at around 18 extra deaths per 100 survivors per year but this decreased to under three extra deaths among those surviving at least five years.

## SOFT TISSUE SARCOMA

### *Fibrosarcoma*

The survival prospects beyond three years have been good for many years. The excess mortality was under one extra death per 200 survivors per year among 10 year survivors.

### *Rhabdomyosarcoma*

Survival beyond three years was slightly poorer than for fibrosarcoma (see table 1). Survival was better for boys than girls. Ten years from three year survival 87% of boys and 74% of girls were still alive. The excess mortality among those who survived at least 10 years was similar to that observed for fibrosarcoma.

## MALIGNANT GONADAL GERM CELL TUMOURS

Survival beyond three years was about 95% 10 years later for both malignant testicular and ovarian germ cell tumours. Survival subsequent to three years for ovarian tumours improved substantially among those diagnosed more recently. Ten years from three year survival 88%, 91%, and 98% of those diagnosed before 1962, between 1962 and 1970, and after 1970 are still alive respectively. Excess mortality among children who had survived at least three years after either a testicular or ovarian tumour was under two extra deaths per 100 survivors per year.

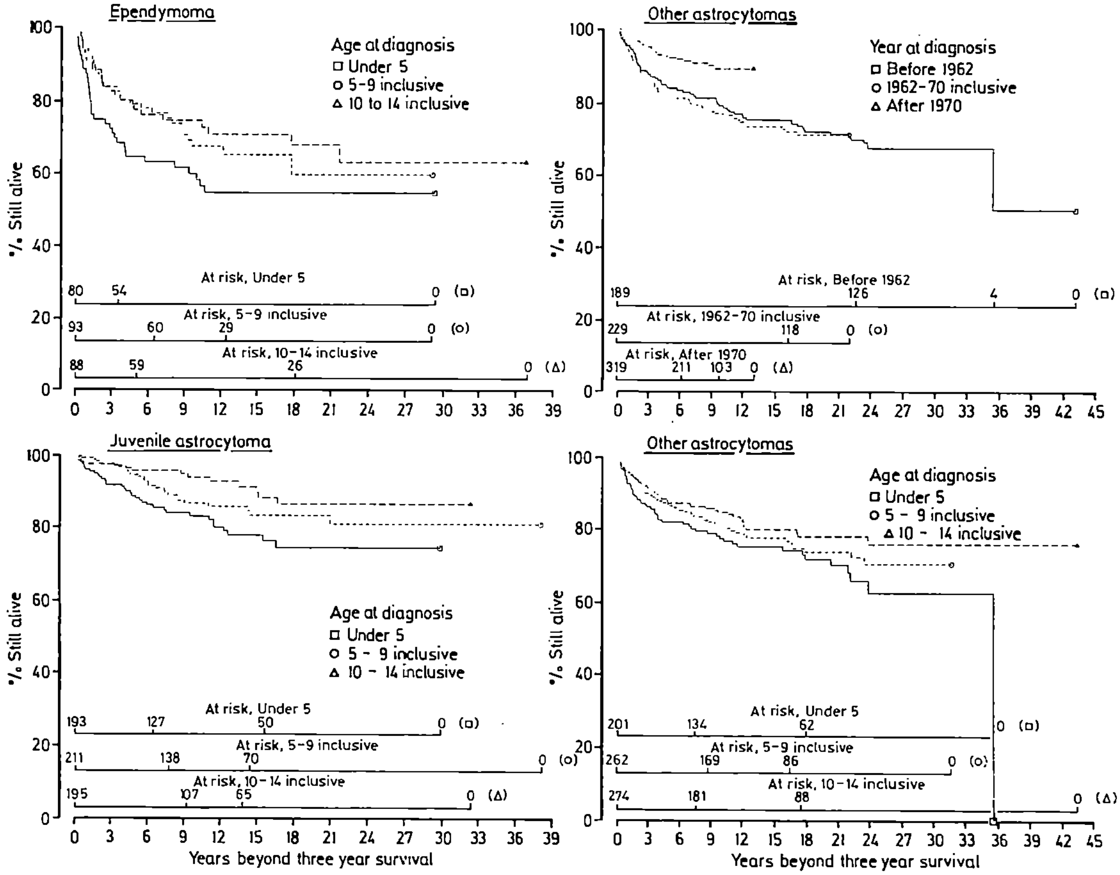
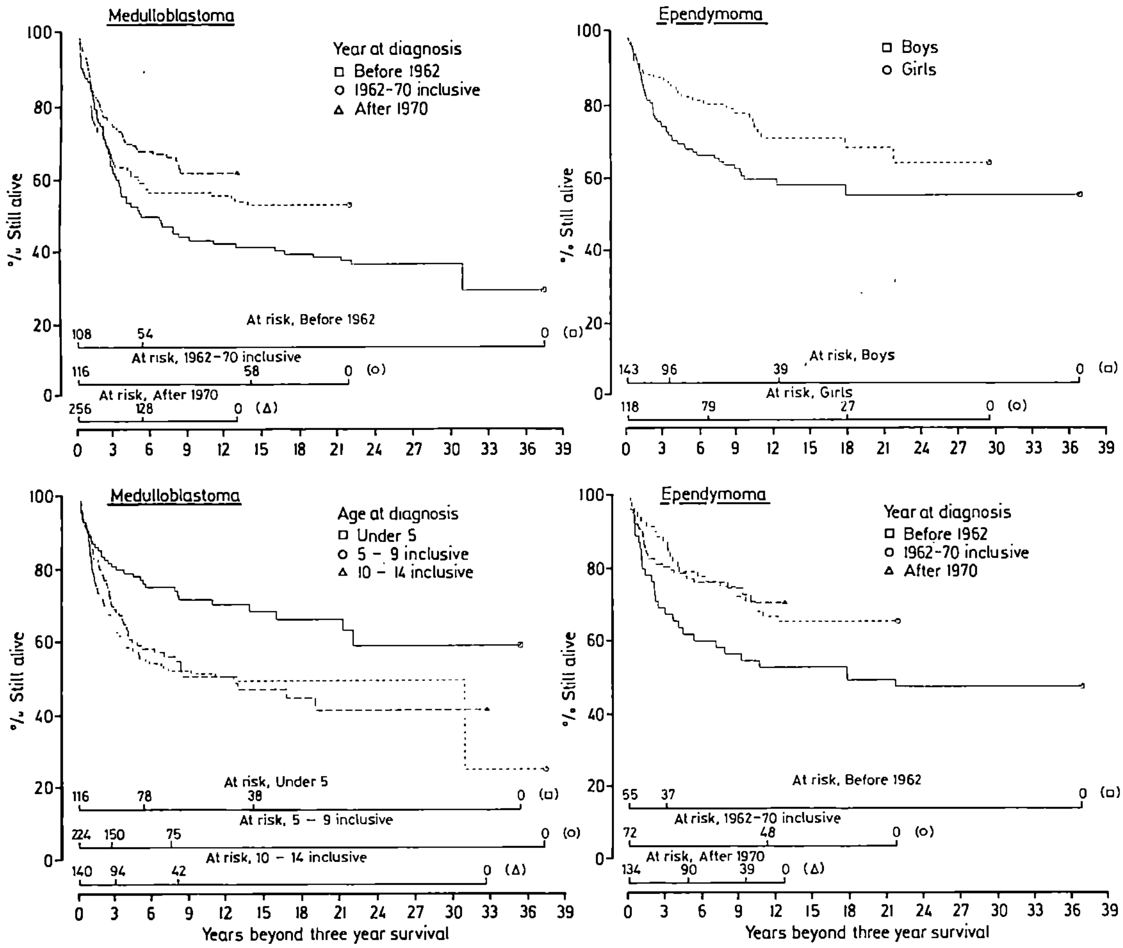


Fig 3 *Long term survival after childhood tumours of the central nervous system.*

## Discussion

With few exceptions[2 7 8] information available on survival after childhood cancer arises either from particular series of cases that are not population based, or from randomised clinical trials. Furthermore, survival is usually examined only in the years immediately after diagnosis. The present study was broadly population based, including the great majority of childhood cancers occurring in Britain. Therefore sufficient cases were available to attempt to examine long term survival and curability in a reliable way. Data were included that relate to survivors diagnosed mostly between 1960 and 1981 and therefore an appreciation of changes in long term survival over time could be obtained. No examination of the effects of treatment was attempted but the considerable improvement in survival subsequent to three years observed for many tumours in more recent years was almost certainly a direct consequence of improved treatment.

No attempt was made to examine the specific causes of death among those who had survived at least three years. The method of assessing evidence of cure compares observed mortality among survivors with that expected from the general population. When there was no statistical evidence of a difference between observed and expected mortality among survivors they were considered cured. Investigators studying evidence concerning the curability of adult cancer have encountered a problem with this method. It has been shown that survivors of several adult cancers including cancer of the breast, cervix uteri, corpus uteri, and ovary may experience similar mortality, from all causes, to that expected from the general population and yet still experience an excess



of deaths from the original cancer when compared with the general population.[9] [10] Other work indicates it is very unlikely that this excess is an artefact of death certification.[11] Therefore our statistical definition of cure may not be the same as clinical cure.[10] It is now well established that survivors of childhood cancer experience a greater risk of a subsequent tumour than expected on the basis of rates of malignant disease occurring in the general population.[12] Therefore an absence of evidence for cure in the statistical sense defined above could arise through an excess of causes other than recurrent tumour and as a result we may underestimate the numbers cured in the clinical sense of absence of recurrent tumour. These possible problems will be considered in a separate paper concentrating on the specific causes of death.

Initially, it is important to examine long term survival, and to compare observed and expected mortality among survivors from all causes of death. This will provide a provisional understanding of the curability of various tumours and the magnitude of any excess mortality in the absence of evidence for cure.

A previous attempt to examine long term survival and cure after childhood cancer, based on substantially fewer cases than available for the present analysis, reported that survivors of several types of childhood tumour experience an excess of mortality when compared with the general population and that an excess persists for at least 20 years from diagnosis for some tumours.[13] In our data survival subsequent to three years improved substantially for acute lymphocytic leukaemia, Hodgkin's disease, and medulloblastoma. Less striking but important improvements have also occurred after Wilms' tumour, ependymoma, other astrocytomas, and malignant ovarian germ cell tumours. The decline in mortality from a range of childhood tumours has been reported from the United States[14] and Italy.[15]

Some of the most interesting comparisons between observed and expected mortality occur more than a decade after diagnosis, where the numbers became rather small, and as a result previous studies were at a serious disadvantage. Although we have relatively large numbers of cases available for analysis there is still a danger of concluding that there is no real difference, because a difference between observed and expected mortality is not significant, when in fact the statistical power of the comparison is low within that particular follow up interval because of a small number of expected deaths. To reduce the possibility of such spurious interpretations the final follow up intervals in table 3, and in any other results reported, have at least 100 survivors still at risk on entry. Evidence of cure is only examined when the expected number of deaths beyond a specified follow up time is at least two. This gives an 80% probability of detecting a mortality rate fourfold that expected using a 5% (one sided) significance level.

Long term survival after the embryonal tumours was always very good in that at least about 90% of three year survivors were alive 10 years later. It has been reported from the United States that over 90% of those surviving at least five years from these embryonal tumours survive a further 10 years.[16] The excess mortality among those surviving at least 10 years after an embryonal tumour never exceeds one extra death per 200 survivors per year. Many of the deaths that occur between five and 20 years from diagnosis of genetic retinoblastoma are likely to be caused by second primary tumours and therefore these are, at least partially, responsible for excess mortality. Late recurrence of neuroblastoma and Wilms' tumour, although rare, have been reported previously.[17 18]

The soft tissue sarcomas were another group with good long term prospects. This is in broad agreement with over 90% of those surviving at least five years remaining alive 10 years later in a study carried out in the United States.[16]

There is a difference in the long term prospects after Hodgkin's disease and non-Hodgkin lymphomas. Ten year survivors of non-Hodgkin lymphomas show evidence of cure, in contrast to those surviving at least 10 years after Hodgkin's disease who experience between one and two extra deaths per 200 survivors per year. It has previously been reported that of those surviving at least five years, 65% of those with Hodgkin's disease, and 90% of those with non-Hodgkin lymphomas were alive 10 years later, based on individuals treated in the United States.[16]

Long term prospects after tumours of the central nervous system vary considerably depending on the type of tumour. At 10 years from three year survival only just over half of those diagnosed with medulloblastoma were still alive, in contrast with almost 90% of those diagnosed with juvenile astrocytoma. Survivors of each central nervous system tumour considered, except medulloblastoma, experienced improved survival subsequent to three years if they were diagnosed when older. In common with neuroblastoma, Wilms' tumour, and Hodgkin's disease survival beyond three years is greater among those diagnosed when younger with medulloblastoma.

Average follow up times after acute leukaemia are still relatively short as these diseases were almost always fatal before the introduction of modern forms of treatment around 1970. Therefore more follow up is needed before a firm assessment of the long term prognosis may be made. Children who had survived at least 10 years after acute lymphocytic leukaemia experienced an excess mortality of just over one extra death per 100 survivors per year. It has previously been suggested that a greater proportion of females with acute lymphocytic leukaemia are cured than are males.[19] In our data the excess death rates were consistently greater among the male survivors.

## Conclusion

After surviving three years, survival prospects are generally very good in that, for most of the childhood tumours considered, over 80% of those surviving at least three years were alive 10 years later. Of the remainder there have been substantial improvements in survival beyond three years after acute lymphocytic leukaemia, Hodgkin's disease, medulloblastoma, and ependymoma where the percentage alive 10 years later among those diagnosed since 1970 are 68%, 87%, 62%, and 73% respectively. This leaves only osteosarcoma and Ewing's tumour where survival subsequent to three years is static at around 77% and 57% alive 10 years later respectively.

Comparing mortality among survivors with that expected showed evidence of cure among survivors of non-Hodgkin lymphomas and non-genetic retinoblastoma. Survivors of other tumours, with sufficient cases surviving beyond 10 years to assess excess mortality, may be considered in two groups. Firstly, those who had survived at least 10 years after neuroblastoma, Wilms' tumour, genetic retinoblastoma, osteosarcoma, fibrosarcoma, or rhabdomyosarcoma never experienced an excess mortality exceeding one extra death per 200 survivors per year.

Secondly, those who had survived at least 10 years after acute lymphocytic leukaemia, Hodgkin's disease, or a tumour of the central nervous system experienced an excess mortality of about one extra death per 100 survivors per year. The excess mortality in both groups was therefore gratifyingly small, particularly among survivors in the former group. The excess mortality among the latter group was similar to that experienced by female survivors of breast cancer subsequent to a recurrence free survival of 15 years.[9]

It is important to continue to monitor the mortality of survivors of childhood cancer for two main reasons: firstly, to examine their mortality when they enter middle age where expected mortality increases; and secondly, to examine long term survival after recently introduced combined forms of treatment for which, as yet, there is a relatively short follow up.

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# Heat stable enterotoxin produced by Escherichia coli in acute diarrhoea

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SUMMARY We screened 569 children with acute onset diarrhoea from five Italian towns for heat stable enterotoxin produced by *Escherichia coli*. We compared an enzyme linked immunoabsorbent assay (ELISA) with the standard suckling mouse assay for detection of the enterotoxin. A total of 31 (5·4%) children were found who had strains of *E coli* that produced heat stable enterotoxin: 26 strains were positive in both tests, four only in the suckling mouse assay, and one only in the ELISA. Compared with the suckling mouse assay the sensitivity of the ELISA was 87% and the specificity was 99·8%. The mean age of the children with *E coli* that produced heat stable enterotoxin was 22 months. Fifteen (48%) of the children had ingested potentially contaminated food and five (17%) had a previous contact with someone with diarrhoea. The clinical picture was milder than that described in developing countries. Faecal osmolality and the osmolal gap were consistent with a secretory diarrhoea in 12 out of 15 (80%) of these children. The mean duration of the diarrhoea was five days. Heat stable enterotoxin produced by *E coli* is a common cause of mild diarrhoeal illness in Italian children.

Diarrhoea induced by heat stable enterotoxin is the result of a multistep process involving (after small intestinal colonisation and release of heat stable enterotoxin[1]) the binding of the toxin to receptors located on the brush border of enterocytes,[2] the activation of the guanylate cyclase-guanosine monophosphate (cGMP) system,[3] and the resulting inhibition of sodium and chloride absorption along with the stimulation of anion and water secretion.[4] Diarrhoea induced by heat stable enterotoxin is therefore of the secretory type, no signs of inflammation or colon involvement being usually present.[5]

*Escherichia coli* that produce heat stable enterotoxin are among the most common aetiological agents of diarrhoea in developing countries.[6–10] Scanty information is available, however, about their role in industralised countries. We have previously reported the isolation of *E coli* that produce heat stable enterotoxin in Naples, southern Italy, from less than 1% of children with acute gastroenteritis in two series of patients.[11 12] A similar frequency has been reported in Brescia, northern Italy.[13] Other investigators reported sporadic isolation from children with diarrhoea in Finland,[14] Canada,[15] and the United States.[16] No strains of *E coli* that produce heat stable enterotoxin have been found in Switzerland[17] or Sweden.[18]

Thus in industrialised countries *E coli* that produce heat stable enterotoxin are regarded as putative agents of traveller's diarrhoea[19] rather than as endemic intestinal pathogens. Accordingly, a search for these agents is not performed on a routine basis in patients with diarrhoea. The identification of heat stable enterotoxin produced by *E coli* is currently based on the suckling mouse assay,[20] which is reliable, does not require special facilities, is relatively inexpensive, but is cumbersome and time consuming. A possible alternative is the use of various DNA probes,[21] which, however, require the use of radioisotopes and might give false positives.[22] Thompson *et al* developed a competitive ELISA for heat stable enterotoxin which is rapid and does not require sophisticated equipment.[23] Until now this test has never been performed on a large number of patients.

As a part of a national investigation on the incidence, aetiology, diagnosis, and clinical features in childhood enteritis by the National Study Group on Acute Diarrhoea in Childhood (coordinated by

S Guandalini), we have screened 569 children with acute onset diarrhoea with the suckling mouse assay and the ELISA for heat stable enterotoxin produced by *E coli*. In the present report we focus on the epidemiological and clinical features of children with *E coli* that produce heat stable enterotoxin and the comparison between the suckling mouse assay and the ELISA for the diagnosis of diarrhoea related to heat stable enterotoxin.

## Patients and methods

A total of 569 children (mean age 43 months, range: newborn to 15 years) from five towns in Italy (Milan, Mantua, Naples, Palermo, and Messina, table 1), who presented with diarrhoea of acute onset, were included in this study. Diarrhoea was defined as an unequivocal greater frequency or diminished consistency of stools, or both, in comparison with the previous usual pattern. Patients known to have received antibiotics were excluded. One hundred and seventy two children without gastrointestinal symptoms, and matched for age and season, were enrolled as controls. Clinical assessment was performed as previously described.[12]

The following information was collected from the parents by the physician in charge of each patient: (a) the presence of subjects with diarrhoea living in the same house in the two weeks before the onset of diarrhoea and (b) the ingestion of food by the patient known to be potentially contaminated and, specifically, uncooked mussels, eggs, and unwashed vegetables. All patients were drinking chlorinated tap water.

### LABORATORY METHODS

Diarrhoea was considered in keeping with a secretory pattern when the osmolal gap [osmolality − 2×(sodium + potassium concentration)] in the stool supernatant did not exceed 40 mmol/l. The isolation and identification of enteropathogens (bacteria, viruses, and parasites) was performed as previously reported.[24] Five strains of *E coli* were pooled from each stool specimen of subjects as well as healthy controls. Strains to be tested for production of heat stable enterotoxin were stored in nutrient agar in the dark and sent to our laboratory in Naples. They were screened by the suckling mouse assay according to Giannella[20]: strains were grown in casamino acid yeast extract in a shaker incubator, the cultures were centrifuged, and 0·1 ml was injected intragastrically in mice 2–4 days of age. After three hours the mice were killed by decapitation and the ratio from gut weight divided by body weight was determined. Values greater than 0·083 were considered positive; values less than 0·075 were considered negative; intermediate results were considered doubtful and repeated. *E coli* strain 214 Cl, which produces heat stable enterotoxin, and an *E coli* strain that does not served as controls.

Table 1 *Isolation rate of E coli that produce heat stable enterotoxin in five Italian towns*

| *Town* | *No (%) children with E coli that produce heat stable enterotoxin/ No of children screened* |
|---|---|
| Milan | 19/201 (9·4) |
| Messina | 1/14 (7·1) |
| Palermo | 6/151 (3·9) |
| Naples | 3/99 (3·0) |
| Mantua | 2/104 (1·9) |
| Total | 31/569 (5·4) |
| Controls | 0/172 |

The same supernatants were simultaneously screened for heat stable enterotoxin using an ELISA test as described by Thompson *et al.*[23] We used antiheat stable enterotoxin monoclonal antibodies prepared against pure heat stable enterotoxin from *E coli* strain 18 D.[25] The standard curve was obtained with heat stable enterotoxin purified by high performance liquid chromatography and quantitated by amino acid analysis. A total of 50 μl of heat stable enterotoxin-bovine serum albumin conjugate (1 μl/mg) in carbonate buffer, ph 9·6, were used to coat each well of a 96 well flat bottom microtitre plate (Limbro Eia Microtest, Flow Laboratories) as suggested.[23] After 18 hours of incubation at 4°C, the plates were washed and subsequently blocked with 1% bovine serum albumin in phosphate buffered saline for one hour at 37°C. An eight point standard curve of pure heat stable enterotoxin was added to each plate. Pure heat stable enterotoxin and samples were mixed with monoclonals (20 C1B8) in glass tubes on ice: each well received 50 μl of monoclonal antibody solution (final dilution 1:160 of 2 μg/ml stock solution) containing 5 μl of bacterial supernatant. After 18 hours of incubation at 4°C, the plates were washed and 50 μl of horseradish peroxidase labelled affinity purified goat antimouse IgG, at a final dilution of 1:250 in 0·1% bovine serum albumin in phosphate buffered saline, were added to each well for 15 minutes at room temperature. Plates were then rinsed and 100 μl of freshly diluted chromogenic substrate (2·2 azino-diethylbenzothiazoline sulphonic acid), with 0·03% hydrogen peroxide in 0·1M citrate buffer, pH 4, were added to each well. After an incubation of 20 minutes in the dark, plates were read by eye. Colour darker than the well containing 100 pg of heat stable enterotoxin (corresponding to 20 ng of heat stable enterotoxin/ml of bacterial culture) were considered positive. Positive strains were tested twice in both the suckling mouse assay and the ELISA.

Both monoclonal antibodies and the heat stable enterotoxin were generous gifts of Dr R Giannella, Cincinnati, Ohio. Culture media were purchased from Difco and antimouse IgG from Kierkegard and Perry. All chemicals were of analytical reagent grade.

Statistical analysis was performed by $\chi^2$ test and by the $t$ test where appropriate.

## Results

*E coli* strains were isolated from 541 of the 569 children with diarrhoea (95%) and from 150 of the 172 controls (87%). A total of 31 (5·4%) children, all belonging to the study group, had strains of *E coli* in their intestine that produced heat stable enterotoxin. These strains were isolated in each of the five towns in which the screening was performed (table 1).

The prevalence of strains of *E coli* that produce heat stable enterotoxin was 11% in children with infectious diarrhoea. They were the fourth most common infectious agent isolated from cases of intestinal infections after rotavirus (47%), campylobacter (17%), and salmonella (15%). In nine affected patients an associated pathogen was isolated: three had rotavirus, two salmonella, two campylobacter, one rotavirus and salmonella, and one rotavirus and campylobacter. A total of 26 strains of *E coli* were positive for heat stable enterotoxin in both ELISA and the suckling mouse assay, one only in the ELISA, four only in the suckling mouse assay (table 2). None of controls was positive for *E coli* that produce heat stable enterotoxin by either assay. Considering the suckling mouse assay as the standard test, specificity of the ELISA was 99·8% and sensitivity was 87%.

Table 2 *Comparison of the ELISA and suckling mouse assay in detecting activity of heat stable enterotoxin*

| | *ELISA positive* | *ELISA negative* |
|---|---|---|
| Suckling mouse assay positive | 26 | 4 |
| Suckling mouse assay negative | 1 | 660* |

*Including 510 patients and 150 controls with *E coli* in the stools.

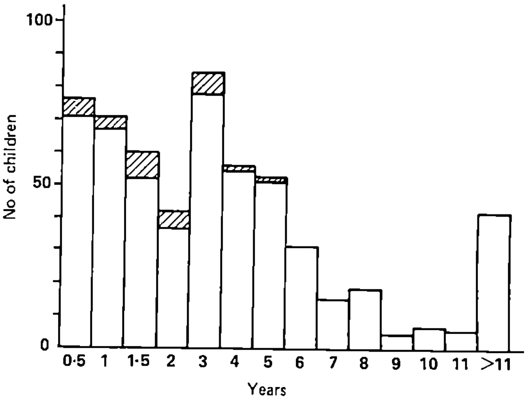

Figure *Age distribution of children with* E coli *that produce heat stable enterotoxin (▨) and of all other patients (☐). The prevalence of diarrhoea induced by heat stable enterotoxin ranged from 5·6% to 13·3% in first 3 years of life and decreased sharply thereafter.*

The seasonal pattern of *E coli* that produce heat stable enterotoxin was as follows: 13 (42%) cases in spring, five (16%) in summer, 12 (39%) in autumn, and one (3%) in winter. The age distribution of the affected children is shown in the figure: the mean age of affected children was 22 months (range 0–63 months) whereas the mean age of all the other children in the study group was 43 months (range 0–180 months) ($p<0{\cdot}05$). A possible interhuman spread of infection was recorded from six (20%) of the patients positive for *E coli* that produce heat stable enterotoxin and from 92 (17%) of all other children with diarrhoea ($p>0{\cdot}05$).

A total of 15 (48%) children with *E coli* that produce heat stable enterotoxin had previously ingested potentially contaminated food one week or less before the onset of symptoms compared with 118 (22%) of all other children enrolled ($p<0{\cdot}01$). Mean duration of diarrhoea was five days (median was 3·2); in 28 of the 31 children, however, symptomatology lasted less than seven days.

Two children were malnourished with weight below the 5th centile.

Clinical features of children with diarrhoea induced by heat stable enterotoxin produced by *E coli* where no other pathogens were found are listed in table 3 and compared with those of all other children belonging to the study group. The incidence of both dehydration and vomiting was significantly lower in children with *E coli* that produce heat stable enterotoxin than in all other patients. On the contrary, there were no differences in the presence of fever, abdominal pain, or associated respiratory symptoms.

In table 4 the stool characteristics of children

Table 3 *Comparison of clinical features of children who were positive or negative for E coli that produce heat stable enterotoxin*

| | *Positive No (%) (n=22)** | *Negative No (%) (n=538)* | *p Value* |
|---|---|---|---|
| Dehydration | 4 (18) | 306 (57) | <0·001 |
| Fever (>38°C) | 5 (23) | 247 (46) | NS |
| Vomiting | 3 (14) | 253 (47) | <0·01 |
| Abdominal pain | 7 (32) | 226 (42) | NS |
| 'Cold' symptoms | 6 (27) | 199 (37) | NS |

Nine children in whom *E coli* that produce heat stable enterotoxin were isolated together with other enteric pathogens were excluded.

Table 4 *Comparison of stool characteristics of children who were positive or negative for E coli that produce heat stable enterotoxin*

| | *Positive No (%) (n=22)** | *Negative No (%) (n=538)* | *p Value* |
|---|---|---|---|
| Watery | 14 (64) | 360 (67) | NS |
| Loose | 8 (36) | 178 (33) | NS |
| Gross blood | 0 (0) | 253 (47) | <0·001 |
| Leucocytes | 1 (5) | 44 (13) | NS |
| Mucous | 6 (27) | 291 (54) | <0·05 |
| Increased osmolal gap | 12/15 (80) | Not performed | |

*Nine children in whom *E coli* that produce heat stable enterotoxin were isolated together with other enteric pathogens were excluded.

positive for and negative for *E coli* that produce heat stable enterotoxin are reported: there were no remarkable differences in the two groups besides the higher incidence of gross blood in the stools of the children who were negative. Determination of sodium, potassium, and osmolality in faeces was performed in 15 subjects: a pattern consistent with secretory diarrhoea was detected in 12 children (80%).

All but five children received oral rehydration only: this consisted of glucose electrolyte (60 mmol sodium) solution. Only one child required intravenous correction of dehydration because of vomiting and severe acidosis.

Antibiotics were given to four children. All patients did well, however, and rapidly regained weight after recovery from the diarrhoea.

In three children the diarrhoea became chronic (>14 days) and the presence of *E coli* that produce heat stable enterotoxin was persistent in the stools, but it ceased spontaneously.

## Discussion

Our data suggest that heat stable enterotoxins produced by *E coli* are a common cause of diarrhoea in paediatric patients in Italy, and that the relative frequency is presently increasing in comparison with the previously available information.[11–13] The decreasing incidence reported in the total number of cases caused by other better known pathogens (probably because of better prevention) is possibly responsible, at least in part, for the observed relative increase in the incidence of diarrhoea caused by heat stable enterotoxin in our country.

Strains of *E coli* that produce heat stable enterotoxin were isolated from all five towns in which the investigation was carried out; this suggests that it is endemic in Italy. No outbreaks occurred during the study period. The history of previous ingestion of potentially contaminated food in about 50% of the affected children suggests that food is likely to be the predominant source of infection. This assumption is supported by previous reports of the role of contaminated food in the endemic and the epidemic spread of enteritis caused by heat stable enterotoxin produced by *E coli*.[26–28]

Transmission through contacts who had diarrhoea is thought to be rare, as a large inoculum is apparently necessary to induce diarrhoea.[29] We have no clear evidence of such a transmission in our series as we did not attempt to isolate *E coli* that produce heat stable enterotoxin from potential contacts. The record of contacts with subjects who had diarrhoea, in any event, in affected patients was similar to that of all children enrolled in the study group.

Spring and autumn peaks in detection were different from that usually reported in developing countries, where the prevalence of isolation is found in the warm and humid season.[27]

The mean age of affected children was younger than that of the study group. The increased susceptibility of young infants to diarrhoea induced by heat stable enterotoxin has been previously reported in developing countries.[6 30] The higher sensitivity of young children to the enterotoxin is supported by recent laboratory investigations. Cohen *et al* have in fact shown in an animal model that the number of receptors for heat stable enterotoxin is increased in young subjects.[31] One of the authors (AG) has reported that in children heat stable enterotoxin produced by *E coli* induces an increase in guanylate cyclase activity, whose magnitude is maximal in the newborn and then decreases with an age related pattern.[32] Therefore the increased susceptibility and severity observed seems to be related to the state of intestinal development.

The overall clinical picture of diarrhoea induced by heat stable enterotoxin was that of a mild to moderate diarrhoea, far less severe than that reported in developing countries. Furthermore, the incidence of dehydration was significantly lower in patients with heat stable enterotoxin produced by *E coli* than in patients with other diagnosis. This was somehow surprising in view of the present understanding of the pathophysiology of diarrhoea mediated by heat stable enterotoxin as a diarrhoea of the secretory type.[33] It should be noted, however, that all patients, with one exception, did well with oral rehydration only. The effectiveness of oral solution in preventing dehydration was due, at least in part, to its prompt administration soon after the onset of diarrhoea. In this respect it is of interest to note that values of faecal sodium and potassium and osmolality were consistent with a secretory diarrhoea in about 80% of our patients.

Mean duration of symptomatology in our study group was not different from that reported in developing countries,[6 34] despite the different incidence of malnutrition in the two population samples. Three children had a protracted diarrhoea, which in one case lasted longer than one month. This unusual presentation of diarrhoea induced by heat stable enterotoxin suggests that the enterotoxin should be considered in the differential diagnosis of chronic diarrhoea.

The reported mortality rate associated with diarrhoea caused by heat stable enterotoxin is variable in developing countries.[35] All of our patients did well thus suggesting that diarrhoea induced by the enterotoxin: (a) does not itself have a high virulence, (b) can be effectively counteracted by prompt rehydration, and (c) is probably less severe in well nourished children.

The ELISA test used was rapid, easy to perform, reliable, and did not require sophisticated equipment. Four strains of *E coli* that produce heat stable enterotoxin were not detected by the ELISA whereas one was positive in the ELISA only. We have characterised an enterotoxin produced by *Klebsiella pneumoniae,* which behaves like the heat stable enterotoxin produced by *E coli,* but is not detected by the ELISA (manuscript in preparation). It is therefore possible that some differences in the primary sequence of the family of heat stable enterotoxins could affect their detection by monoclonal antibodies raised against pure heat stable enterotoxin from *E coli.* We do not have an explanation for the strain that was positive exclusively in the ELISA.

Even though the ELISA test did not detect about 10% of the heat stable enterotoxins detected by the suckling mouse assay, we believe that this is a good alternative to the latter and to the DNA probe, particularly when large numbers of samples are to be screened or if animals or radioisotopes are not available.

## Conclusion

Heat stable enterotoxin produced by *E coli* is a common cause of acute watery diarrhoea in Italy. Contaminated food is likely to be the main source of infection. Younger infants are more susceptible to diarrhoea caused by heat stable enterotoxin produced by *E coli.* The symptomatology is usually milder in Italy than that described in developing countries. The symptomatology is milder than that associated with other aetiologies. Heat stable enterotoxin can be responsible for chronic diarrhoea. The ELISA test with monoclonal antibodies is a convenient and reliable tool for diagnosis.

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# Cerebrospinal fluid pressure in pyogenic meningitis

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SUMMARY The pressure of cerebrospinal fluid taken at lumbar puncture was recorded objectively by strain gauge pressure measurement in 35 infants and children with pyogenic meningitis. Raised pressures were found in 33 children. The median pressure was 15 mm Hg (range 4–70 mm Hg) in all age groups. The pressure level varied throughout the infection, but a higher median pressure (19 mm Hg) was found when this was measured on the day of admission. The clinical features of the meningitis in these patients suggest that many of the presenting symptoms and signs are those of pressure. These results show that high pressure is frequently present in childhood meningitis, not just in those who die from cones or who have radiological evidence of hydrocephalus. We conclude that raised cerebrospinal fluid pressure is a frequent accompaniment of childhood meningitis and may need treatment in its own right and is therefore one further important factor influencing the course and outcome of childhood meningitis.

The outcome from bacterial meningitis in infancy and childhood has not significantly improved over the last 15 years. In a series from Boston there was a mortality of 6·4% for all types of meningitis in infancy and childhood.[1] A recent report from the United Kingdom found an 8·6% mortality from bacterial meningitis in the first year of life.[2]

One possible cause for therapeutic failure and this morbidity and mortality may be the failure to recognise and treat accompanying raised intracranial pressure with its effect of impairing cerebral blood flow with subsequent ischaemia. Brain swelling has been recognised as an important contributing factor to the mortality and morbidity in some cases of pyogenic meningitis.[3] It has been suggested that monitoring cerebrospinal fluid pressure and aggressive treatment could be crucial to survival in selected cases of meningitis which had clinical features of raised intracranial pressure.[4] Evidence, however, for raised pressure in pyogenic meningitis has relied largely upon necropsy reports of brain swelling and cones. In a review of the literature Addy deduced that coning may contribute to the outcome in perhaps 30% or more deaths from meningitis.[5]

Direct measurement has been undertaken in severely ill ventilated children with infections of the central nervous system, 11 of whom had meningitis.[6] For these 11 comatose patients the maximum intracranial pressure was 47 mm Hg and the minimum cerebral perfusion pressure 30 mm Hg. Only four were normal on long term follow up and the author considered a cerebral perfusion pressure greater than 30 mm Hg a significant pointer to survival.

This paper is a descriptive account of the intracranial pressure (and the cerebral perfusion pressure) from direct lumbar puncture recordings, with a non-fluid displacement method, in 35 infants and children with different types of pyogenic meningitis.

## Patients and methods

The patients were all treated at the Royal Hospital for Sick Children, Edinburgh, in the neurology unit. There were 35 children who had pressure in the lumbar cerebrospinal fluid measured in the course of pyogenic meningitis. Their median age was 10 months ranging from 1 month to 13 years; 18 were infants. There were 23 boys and 12 girls. The patients included in this study were both selected and unselected: they were selected in that the neurology unit at this hospital does not see all admitted patients with pyogenic meningitis, and frequently only sees pyogenic meningitis with neurological complications. Eight of these patients had already commenced antibiotic treatment when transferred from another hospital or unit. They were unselected in that all available pressure recordings of lumbar cerebrospinal fluid obtained in patients with pyogenic meningitis over the last eight years were included in this study.

From the onset of symptoms until pressure recording of lumbar cerebrospinal fluid, there was a median of three days (range of 0·5 days to 21 days). This pressure recording was the first lumbar puncture (that is, in which the diagnosis of meningitis was made) in 28 cases and was a subsequent lumbar puncture recording in seven patients. The time between admission to hospital and this pressure recording ranged from 0–13 days. Twenty two of the 35 patients' recordings were from lumbar puncture on the day of admission.

### TECHNIQUE

The cerebrospinal fluid pressure recordings were obtained at the time of lumbar puncture. We used a non-displacement method of measuring the cerebrospinal fluid pressure by connecting a strain gauge pressure transducer (attached to a three way tap) to the end of the spinal needle when the stilette had been removed and the cerebrospinal fluid had reached the mouth of the needle.[7] The presence of a pulse wave verified the position of the spinal needle and showed the respiratory and cardiac component of the pressure wave.

The strain gauge transducer was calibrated before procedure with a sphygmomanometer over a range of 0–50 mm Hg. The transducer was then sterilised in a 2% solution of glutaraldehyde (Cidex). The signal from the transducer was written out as a permanent record on a physiological pen recorder. A minute or more of recording was obtained while the patient was permitted to relax a little with slightly reduced flexion, with the head and neck in a neutral position and no undue abdominal compression. After a few minutes, the patient relaxed and the pressure dropped to its true height. At this level with free communication in the cerebrospinal fluid spaces, the pressure of the lumbar cerebrospinal fluid reflected the intracranial pressure.

These pressure recordings of lumbar cerebrospinal fluid were only obtained in situations where a lumbar puncture was indicated and clearly would not be obtained where there were absolute contraindications to doing a lumbar puncture in the first place (such as a coma, decerebration, papilloedema, retinal haemorrhages, evidence of space occupation, etc) without first scanning the patient. This method of lumbar pressure recording was both more accurate and potentially safer than the older open ended manometric methods. It was more accurate in that cerebrospinal fluid was not displaced from a closed craniovertebral axis into a capillary column in order to measure the pressure. It was potentially safer in that if high pressure was found, then without removing cerebrospinal fluid, mannitol (7 ml/kg of 20% solution) and frusemide (1 mg/kg) could be given with an immediate effect on the cerebrospinal fluid pressure.

The signs and symptoms of raised intracranial pressure are known to be unreliable, variable, unusual, and even absent.[8] A tense anterior fontanelle does not show the extent to which the pressure is raised,[9] whereas direct measurement is unequivocal, therefore if coma was present (to the extent of failure to localise pain) a computed tomogram was performed to determine if the basal cisterns were open and there was no space occupation. Should a subsequent lumbar puncture be necessary in the course of treatment of meningitis, or if intrathecal antibiotics were being used, then lumbar puncture pressures were recorded on each occasion.

Before lumbar puncture a blood pressure measurement was obtained by conventional sphygmomanometer cuff on the upper limb. This allowed calculation of a single cerebral perfusion pressure value using the classical method—that is, by subtraction of the mean cerebrospinal fluid pressure from the mean systemic blood pressure.

## Results

A positive bacteriological identification of the infecting organism was made in 26 cases: seven were due to meningococcal meningitis, 11 to *Haemophilus influenzae,* four to pneumococcus, one to tuberculous meningitis, one patient had two organisms (meningococcus and haemophilus), one a pasteurella organism, and one a coliform. Four further cases were partially treated on admission and no organism cultured. Five further cases were clinically recognised as meningococcal without bacteriological confirmation.

The clinical presentation of the symptoms and signs that were apparent at any stage during the course of the pyogenic meningitis are shown in table 1.

Brain imaging by either ultrasound scanning or computed tomography was not available on all patients at a consistent time in the course of the meningitis but on 10 occasions there were abnormal imaging results in the form of oedema, dilatation of the lateral and third ventricles, subdural effusions or collections and tight ventricles from oedema. An increase in the size of the subarachnoid space together with an increased echogenicity of the interhemispheric convolutions, and increased parenchymal echogenicity as previously described,[10] was a not infrequent appearance.

Fifteen of these 35 patients had the pressure of their lumbar cerebrospinal fluid measured while having mannitol or immediately after the administration of mannitol. Twenty did not have mannitol at the time of this lumbar puncture recording. Only two of these 35 children had an intracranial pressure measurement that could be considered in the normal range for age (as defined in table 2). The normal range of pressure was calculated by an extensive literature search and the upper limit defined for neonates, infants, children (up to 14 years), and adults. On this basis, only two children had intracranial pressure measurements in the normal range and one of these was on the 17th day of the child's illness, three days after admission to hospital. The other was in the intensive care unit and it was seven days after admission when this pressure recording was obtained.

The median and range of lumbar cerebrospinal fluid pressure measurements are shown in table 3. These values are higher than the expected mean cerebrospinal fluid pressure values in normal individuals. The 35 cerebrospinal fluid pressure values from 35 children with pyogenic meningitis are contrasted with normal intracranial pressure upper limits extracted from the literature and shown in fig 1. Blood pressure measurement before lumbar

Table 1 *Frequency of symptoms and signs in 35 cases of pyogenic meningitis*

| | *No of children* |
|---|---|
| **Symptoms:** | |
| Fever | 31 |
| Headache/irritability | 29 |
| Vomiting | 22 |
| Anorexia | 17 |
| Seizure | 14 |
| Lethargy | 10 |
| Diarrhoea | 9 |
| Photophobia | 5 |
| Stridor | 4 |
| **Signs:** | |
| Neck stiffness | 22 |
| Drowsiness | 21 |
| Respiratory dysfunction | 19 |
| Abnormal tone | 18 |
| Pallor | 18 |
| Tense anterior fontanelle | 13 |
| Rash | 12 |
| Opisthotonos | 11 |
| Squint | 8 |
| Positive Kernig's sign | 8 |
| Papilloedema | 8 |

Table 2 *Mean upper limit of normal intracranial pressure derived from studies where intracranial pressure was objectively measured*

| | *Normal pressure (mm Hg)* | *Method* | *Mean upper normal limit (mm Hg)* |
|---|---|---|---|
| **Neonates:** | | | |
| Welch 1980[11] | 0·29–4·41 | Fontanometry | <3·5 |
| Welch 1978[12] | <2·94 | Fontanometry | |
| Kaiser and Whitelaw 1986[13] | 2·8 (1·4) (SD) | Lumbar puncture | |
| Gerlach *et al* 1967[14] | 0·74–1·03 | Lumbar puncture | |
| **Infants:** | | | |
| Welch 1980[11] | 1·84–12·15 | Fontanometry | <5·8 |
| Gaab *et al* 1980[15] | 5 (2) (SD) | Fontanometry | |
| von Wild and Porksen 1980[16] | −2–5 | Fontanometry | |
| Sidbury 1920[17] | 2·21–5·15 | Lumbar puncture | |
| Levinson 1928[18] | 1·47–5·15 | Lumbar puncture | |
| Munro 1928[19] | 2·12–5·88 | Lumbar puncture | |
| **Children:** | | | |
| Quincke 1891[20] | 2·94–4·41 | Lumbar puncture | <6·4 |
| Levinson 1923[21] | 3·31–6·99 | Lumbar puncture | |
| Levinson 1928[18] | 2·94–5·88 | Lumbar puncture | |
| Lups and Haan 1954[22] | 2·94–7·35 | Lumbar puncture | |
| Gerlach *et al* 1967[14] | 2·94–7·35 | Lumbar puncture | |
| **Adults:** | | | |
| Merritt and Fremont-Smith 1937[23] | <13·24 | Lumbar puncture | <15·3 |
| Masserman 1934[24] | 10·9 (2·5) (SD) | Lumbar puncture | |
| Masserman 1935[25] | 11·1 (2·1) (SD) | Lumbar puncture | |
| Spina-Franca 1963[26] | 3–14·5 | Cisternal puncture | |
| Tourtellotte *et al* 1964[27] | 11 (2·4) (SD) | Lumbar puncture | |
| Gilland *et al* 1974[28] | 11·5 (2·6) (SD) | Lumbar puncture | |
| Ekstedt 1978[29] | 10·3 (1·5) (SD) | Lumbar puncture | |
| Ferris 1941[30] | <17·6 | Lumbar puncture | |

Table 3 *Median and range of cerebrospinal fluid pressures in patients with pyogenic meningitis*

| | *No of patients* | *Median (range) cerebrospinal fluid pressure (mm Hg)* |
|---|---|---|
| All patients | 35 | 15 (4–70) |
| At diagnostic lumbar puncture | 28 | 15 (8–70) |
| Aged<1 year | 18 | 15 (4–28) |
| Aged>1 year | 17 | 15 (5–70) |
| Aged>1 year and at diagnostic lumbar puncture | 15 | 15 (8–70) |
| Aged>1 year with lumbar puncture on day of admission | 10 | 19 (8–70) |

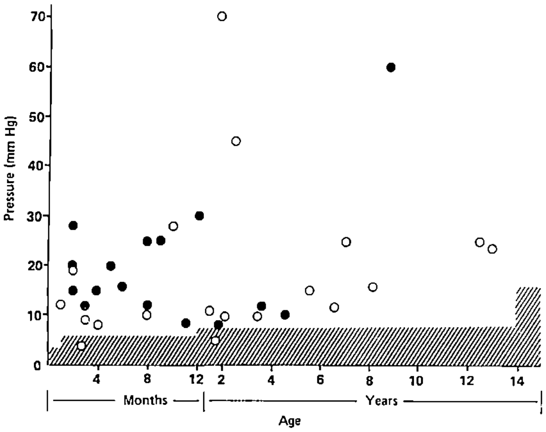

Fig 1 *Cerebrospinal fluid pressure measurements from 35 children with pyogenic meningitis compared with the normal upper limits as previously defined. (○)=pressure level without mannitol. (●)=pressure level after mannitol plus frusemide.*

puncture was available on 33 children. The mean (SD) systemic blood pressure was 80·5 (11·9) mm Hg. The cerebral perfusion pressure was calculated individually on 33 children and the median pressure was 65 mm Hg (range 8–88 mm Hg) when a raised cerebrospinal fluid pressure was present. There was no correlation between the levels of pressure and the cell counts, or cerebrospinal fluid protein concentrations.

The outcome categories are those suggested by Seshia *et al* with five grades of outcome: 1, normal; 2, mild handicap as suggested by minimal alterations of tone, reflexes, an isolated cranial nerve palsy, mild weakness or ataxia, moderate handicap; 3, moderate weakness or ataxia, behaviour disturbance, cranial nerve involvement; 4, severe handicap, severe weakness or ataxia, tetraplegia; and 5, death.[31] In terms of development state, grade 1 was normal, grade 2 was mild handicap, grade 3 was moderate handicap, grade 4 was profound handicap, and grade 5 was death.

There were no deaths in this series. Twenty four of these children with pyogenic meningitis were neurodevelopmentally normal at the time of follow up, and eight had a minimal handicap (one was delayed slightly in development, one had mild hypotonia, three had squints, two had mild deafness, and one had controlled seizures). Three children suffered severe handicap (one was deaf, blind and mentally handicapped with hydrocephalus, a second was hydrocephalic, deaf, blind, had seizures and cerebral palsy, and the third had severe cerebral palsy, epilepsy, and choreoathetosis). The period of follow up was from one month to six years 10 months, a median follow up of one year and one month. As might be expected there was no correlation between mean intracranial pressure or cerebral perfusion pressure measurements and outcome, nor between the cells or protein in the cerebrospinal fluid and outcome. In particular, there was no correlation of age with outcome.

## Discussion

A single pressure recording of lumbar cerebrospinal fluid was made in each of the 35 children with pyogenic meningitis. These values were raised in 33 of the 35 cases when compared with normal pressures ascertained by an exhaustive literature search of papers where the cerebrospinal fluid pressure was directly measured.

This rise in lumbar cerebrospinal fluid pressure was despite the fact that some of these lumbar pressure recordings were measured at diagnostic lumbar puncture, after mannitol administration, or after commencement of treatment. The median pressure of lumbar cerebrospinal fluid was 15 mm Hg (4–70 mm Hg) with a slightly higher value for meningitis after 12 months of age when children had a pressure recording early in the course of their meningitis of 19 mm Hg (8–70 mm Hg). The range of this pressure rise was up to 70 mm Hg in one case (patient not given mannitol). It could reasonably be assumed that the 15 patients who had their cerebrospinal fluid pressures measured immediately after mannitol would have had considerably higher cerebrospinal fluid pressures had mannitol not been given. Daily or sequential pressure measurements were obtained in only a few children and apart from the frequent finding of raised pressure early in meningitis, raised pressures were frequently found at other times and could vary significantly from day to day.

Although the normal values are quoted in the literature, most clinicians use as a rule of thumb a normal intracranial pressure of adults and older children as being less than 10 mm Hg with values of 10–20 mm Hg thought to be raised but not requiring any treatment and those values above 20 mm Hg as being unequivocally raised. In this whole series 13 cases had intracranial pressure levels of 20 mm Hg or more and in children over the age of 12 months, all but two had values in excess of 10 mm Hg.

Simultaneous blood pressure measurements allowed a cerebral perfusion pressure to be calculated but despite the high cerebrospinal fluid pressure, the cerebral perfusion pressure values in only two children were below acceptable levels of 30 mm Hg. It is suggested that cerebral autoregulatory mechanisms are non-functioning in severe infections of the central nervous system in which case the cerebral blood flow is passively dependent on the systemic blood pressure maintaining a cerebral perfusion pressure. The high cerebral perfusion pressures (despite the fact that they are single measurements) in this study reflect a Cushing effect of an increase in systemic blood pressure secondary to raised intracranial pressure, which is a compensatory mechanism which maintains an adequate perfusion pressure despite a raised intracranial pressure.

'C waves' were originally described as spontaneous fluctuations in the intracranial pressure signal occurring at 6/minute (range 4–8).[32] 'C waves' have not previously been reported in meningitis but occurred in eight patients in our series (fig 2). It has been postulated that they reflect Traube-Hering-Mayer vasomotor waves that occur in the systemic blood pressure. They are part of the Cushing phenomena and occur with raised intracranial pressure. An intact Cushing response is a protective mechanism to maintain cerebral perfusion pressure and the frequent observation of these 'C waves' in our recordings is consistent with there being a high cerebral perfusion pressure.

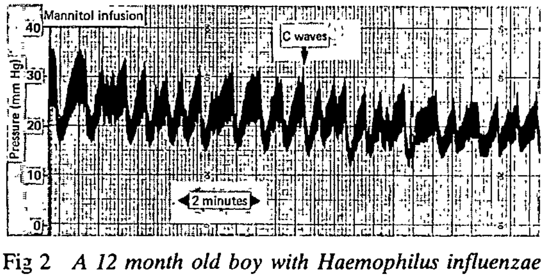

Fig 2 *A 12 month old boy with Haemophilus influenzae infection who was given mannitol during recording of cerebrospinal fluid pressure at lumbar puncture, with a slow return of the pressure from 30 mm Hg to normal, and who required intravenous frusemide. The recording shows typical 'C waves' with a ramped appearance.*

THEORETICAL REASONS FOR RAISED PRESSURE

These results suggest that a raised cerebrospinal fluid pressure is much more common than has been suggested by the number of meningitic deaths from pressure coning. There are several possible theoretical reasons to explain rises of the cerebrospinal fluid pressure: (a) arachnoid granulations become occluded; (b) constriction and strangulation of cerebral veins; (c) cerebritis; and (d) a generalised inflammatory brain oedema; (e) adhesive formation at the base of the brain; (f) inappropriate secretion of antidiuretic hormone; (g) subdural effusions or haematoma or abscesses; (h) major seizures or status epilepticus[33]; and (i) an increase in cerebrospinal fluid production.

We have observed that the response to mannitol varies. In some patients the raised pressure may take 25 minutes to return to normal values, while in other cases (fig 3) the response is more dramatic, suggesting that different pathological mechanisms are responsible for the oedema or hydrocephalus in different patients. It is possible that more than one of the above mechanisms may be operative in any one patient. As there were only 15 patients who received mannitol, the precise intracranial pressure response in patients with pyogenic meningitis would require investigation in a larger series. No one type of organism resulted in pressure significantly different from another, that is, haemophilus, meningococcus, or pneumococcus were not more prone to higher pressures in this series.

CLINICAL FEATURES OF MENINGITIS AND PRESSURE

Many of the clinical features in this series (tense

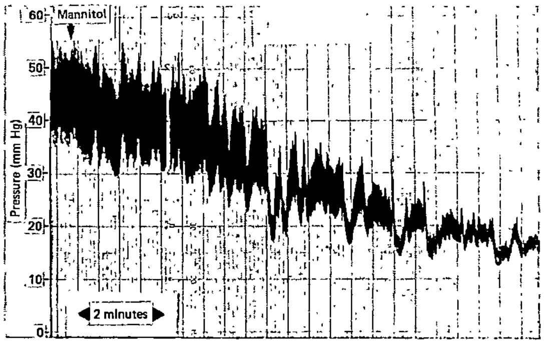

Fig 3 *A 2½ year old boy with meningococcal meningitis and septicaemia whose cerebrospinal fluid pressure at lumbar puncture decreased from 43 mm Hg to normal values in approximately 12 minutes with mannitol infusion.*

fontanelle, squint, neck stiffness, posturing, vital sign abnormalities, opisthotonos, and papilloedema) are in fact signs of raised intracranial pressure, although they are traditionally thought of as signs of meningeal infection. Our observation of frequent raised pressure would confirm some of the clinical features as pressure signs more than infection signs.

### IMPORTANCE OF RAISED PRESSURE (IMMEDIATE AND LONG TERM)

The question of the importance of raised cerebrospinal fluid pressure is more difficult to prove. In the short term these children on presentation are frequently irritable, resent handling, have vital sign abnormalities, pupillary abnormalities, etc, and after the administration of mannitol there is almost always an improvement in these signs and the patients' general responsiveness, confirming that it is often the pressure which is responsible for the clinical picture. Observations similar to these were made by Williams *et al* who used hypertonic intravenous urea and found a dramatic improvement in respiration, conscious state, pupillary signs, and cessation of fits.[3] There were no children who developed subdural effusions in this series as a result of a rapid diminution of brain volume from mannitol and frusemide.

In the long term all that can be said is that treatment of raised intracranial pressure may lessen the neurological complications of meningitis. It would not be possible having measured a raised cerebrospinal fluid pressure, not to do anything about it in an individual child, and yet there seems little hope of proving its importance without a controlled trial of treatment for raised pressure.

As there are multiple factors likely to influence outcome, one would not expect with 35 patients to see a statistical association between the level of intracranial pressure (or cerebral perfusion pressure) and outcome. What is important, however, is that there was no mortality in this group and the overall morbidity and mortality for meningitis was less than expected from the current literature. Eleven children (31%) in this series had some sequelae, eight of these were minimal (four with squints, two with mild hearing impairments, one mildly clumsy, one with two fits within one month of completing treatment), and three children had severe neurological deficits (8·6%). The period to follow up, however, in some cases was quite short and ranged from one month to six years and 10 months with a median of one year one month. Therefore, mild neurological sequelae may not yet be apparent in some of these younger children (for example, clumsiness).

The effect of raised intracranial pressure is to reduce cerebral perfusion pressure and produce ischaemia as well as produce brain shifts and cones. It may be that management of raised pressure in meningitis will have a more dramatic effect on mortality than morbidity as the cerebral perfusion pressure was largely preserved in these patients.

Postmortem examinations of children who had meningitis have shown evidence of pressure (with brain stem compression, swollen oedematous brain, diminished ventricular size, bilateral grooving of the uncal gyri, and rostrocaudal brain stem compression) and scanning has shown hydrocephalus or oedema. Our results show the very frequent accompaniment of raised cerebrospinal fluid pressure with pyogenic meningitis, but our hypothesis remains, that raised pressure is but one important factor influencing the outcome of childhood meningitis.

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# Intermittent catheterisation for neuropathic urinary incontinence

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SUMMARY Eighty six children with neuropathic urinary incontinence who had been treated by clean intermittent catheterisation for more than five years were reviewed. Eighty five had congenital lesions, and one traumatic paraplegia. During the day, 72 (84%) patients were dry or had minor stress incontinence only, 11 were damp but controlled with pads, and only three were continuously wet. Eleven abandoned clean intermittent catheterisation, five because of poor control, four by choice despite good control, and only two because of deterioration of upper urinary tract disease. Most of them usually had bacteriuria, but only 32 developed occasional symptomatic infections. Urinary calculi occurred in six, epididymitis in three, and urethral problems in four. Upper urinary tract dilatation did not arise in a previously normal renal system in any patient during clean intermittent catheterisation.

Clean intermittent catheterisation was successful in controlling wetting with few serious complications, and was well tolerated. It remains the method of choice for the management of neuropathic urinary incontinence in such children.

Intermittent catheterisation as a method of managing early urinary retention after traumatic spinal cord lesions was advocated by Guttmann and Frankel.[1] Lapides *et al* subsequently described the technique of clean intermittent catheterisation for long term management of neuropathic urinary incontinence. This was based on the concept that regular complete bladder emptying was more important than sterile technique in preventing symptomatic urinary tract infection.[2] Many patients have since been managed successfully in this way, without the need for cumbersome appliances.

There have been many reports of the use of clean intermittent catheterisation in children with myelomeningocele, and the early results have been good.[3-6] This early experience has suggested that it is associated with a lower incidence of renal complications than urinary diversion[7 8] and is the method of choice for managing children with neuropathic urinary incontinence, at least in the short term.

The aim of this study was to assess the practicability, efficacy, safety, and acceptability of long term clean intermittent catheterisation in children who had been treated for at least five years in this way.

## Patients and methods

All children with neuropathic urinary incontinence who started clean intermittent catheterisation in this centre between 1977 and 1981 were studied.

Before starting the treatment each patient had an intravenous urogram, a micturating cystogram, and a cystometrogram. This enabled assessment of upper urinary tract dilatation and function, bladder and urethral function, and vesicoureteric reflux. Cystometrography was initially carried out using a simple technique with a balloon catheter connected to a central venous pressure manometer. Later, a size 5 FG side hole catheter connected to a strain guage was used to measure bladder pressure during filling through a second 5 FG catheter passed alongside it. Radiographic contrast was used, and the bladder screened during filling to determine the association between vesicoureteric reflux and pressure. Urethral pressure profiles were measured by taking a continuous pressure recording as the catheter was withdrawn slowly from an empty bladder while simultaneously injecting at 1 ml/minute.

The patients and their parents were trained to catheterise using a clean but not sterile technique, as previously described.[5] They were taught to pass the catheter by touch, and thus many were able to manage clean intermittent catheterisation despite severe deformity and visual handicap. Girls used firm polyethylene catheters and boys used Nelaton catheters. They were taught to rinse the catheter in fresh running tap water before and after use, and soak it in sodium hypochlorite solution overnight.

Patients were followed up at intervals of three months, and a sample of urine was taken for microscopy and bacterial culture at each visit. Prophylactic antibiotics were not used routinely. Intravenous urography was repeated every three years to reassess the condition of the upper urinary tracts. Further investigations were ordered as clinically indicated. In addition the patients were recalled to a specially arranged clinic for the purpose of this study at the end of the study period.

## Results

A total of 86 children started clean intermittent catheterisation for incontinence during this period, and have been followed up for five to nine years. There were 46 boys and 40 girls, median age 11 years (range 4–16 years). Most had neural tube defects (80 myelomeningoceles, and three lipomeningoceles), one had sacral agenesis, one traumatic paraplegia, and one had an idiopathic neurogenic bladder. Forty had a sensory level above T12, 22 between L1 and L4, and 24 had sacral lesions. Thirteen were totally confined to wheelchairs, and 52 had limited mobility with calipers and crutches. Only 13 were able to walk without any form of appliance. Eight required some appliance or had markedly abnormal gait. Many had mild mental handicap, although only four were so severely affected as to be unable to be taught to catheterise themselves.

Before starting catheterisation 55 were using pads and diapers, 22 external appliances, 12 manual expression, four indwelling catheters, and one had had reversal of an ileal conduit urine diversion.

Seventy eight (91%) had learned to catheterise themselves within two years of starting. Most catheterised every two to four hours during the day at regular intervals, but 30 recognised vague symptoms from bladder distension that helped them time the clean intermittent catheterisation. Only five woke up at night to catheterise. Older patients learned to catheterise more often while out drinking in the evenings. Girls found it more difficult to control incontinence during menstruation.

Twenty six patients (30%) were completely dry day and night. Fifty (58%) were completely dry during the day, and 22 (26%) had minor stress incontinence only. Only three patients had problems with severe daytime wetting that was not controlled by catheterisation and pads. At night 32 were dry, and only 11 wet their bedclothes despite the use of pads.

Because of poor control despite two hourly catheterisation, 48 patients were tried on drugs (propanthelene bromide, imipramine, or oxybutynin). Improvement was recorded in 38. Side effects required reduction of the dose or the stopping of the drug in only five.

Symptomatic urinary tract infections were recorded occasionally in only 32 patients, though all but one frequently had bacteriuria and pyuria. Their symptoms were usually vague, consisting of general malaise, fever, discomfort during catheterisation, and poorer control of incontinence. Eight patients reported difficulty with inserting the catheter caused either by bladder neck spasm, balanitis, erections, or difficulty with balance. Two patients developed renal calculi and two had bladder calculi. Two further patients developed bladder stones along suture lines after bladder augmentation. Three boys had epididymitis, two had recurrent episodes of urethral bleeding, one developed a urethral stricture, and one a posterior urethral diverticulum.

Thirty two patients had hydronephrosis before starting clean intermittent catheterisation. On serial intravenous urography this was shown to improve in 13, even in the presence of vesicoureteric reflux (table 1). Unilateral dilatation deteriorated in one patient with reflux after colonic bladder augmentation. Deterioration in two patients without reflux was attributed to poor bladder emptying. This was the result of catheter impaction in a posterior urethral diverticulum in one, and poor compliance in the other who was unable to catheterise himself more than twice daily. There was no radiographic evidence of deterioration in four patients who had reflux without dilatation before starting clean intermittent catheterisation, and dilatation did not arise in any previously normal renal system during catheterisation.

Initial urodynamic studies had little predictive value for these patients, but were useful in selecting those who could be helped by drugs. For the whole group, median bladder volume was 200 ml (range 25–300), bladder pressure 20 mm Hg (range 5–60), and urethral resistance 26 mm Hg (range 5–60). There was no significant correlation between any of these measurements before starting clean inter-

Table 1 *Outcome in patients with upper urinary tract dilatation before starting clean intermittent catheterisation*

| *Outcome* | *No with reflux* | *No without reflux* |
|---|---|---|
| No change | 6 | 10 |
| Improvement | 7 | 6 |
| Deterioration | 1 | 2 |
| Total | 14 | 18 |

mittent catheterisation, and the final result in terms of continence and upper tract deterioration. Continence did improve in many who persevered, and urodynamic studies were not repeated routinely in such patients.

Nineteen patients underwent further urinary tract surgery after starting clean intermittent catheterisation (table 2). Bladder augmentation was successful in increasing bladder volume in all four patients, but failed to improve continence in two of them. Two of those who had artificial urethral sphincters were active paraplegic athletes who, although they had only minor stress incontinence, found that this severely limited their activities. Two boys whose bladder neck spasm made catheterisation difficult underwent transurethral sphincterotomy: one remained dry after the procedure and the other, who was damp before, was not made any worse. Two patients had nephrectomies, one for pyonephrosis secondary to renal calculi, and one for a nonfunctioning kidney secondary to obstruction by a bladder diverticulum present before starting clean intermittent catheterisation. The need for nephrectomy was not attributable to catheterisation in either patient. One patient has since had an ileal conduit urinary diversion in another centre after discharge from our clinic, although his incontinence was well controlled with catheterisation without upper urinary tract deterioration. One has had a perineal urethrostomy after developing a urethral stricture, and has since changed to indwelling catheter drainage (two years after starting clean intermittent catheterisation). One, in chronic renal failure before starting clean intermittent catheterisation, had a renal transplant.

Six patients died during the study period. One boy died at home aged 17, after four years of clean intermittent catheterisation. A diagnosis of renal failure secondary to bilateral hydronephrosis and infection was made at necropsy. He had undergone transurethral sphincterotomy at the age of 5 for hydronephrosis, and had unilateral grade 2 vesicoureteric reflux when he started clean intermittent catheterisation. Another died during a rejection episode after renal transplantation. Two died from chest infections and two from the complications of hydrocephalus.

Table 2 *Urinary tract operations carried out after starting clean intermittent catheterisation*

| *Operation* | *No of patients* |
|---|---|
| Colovesicoplasty | 4 |
| Artificial urethral sphincter | 3 |
| Circumcision | 3 |
| Sphincterotomy | 2 |
| Nephrectomy | 2 |
| Ileal conduit diversion | 1 |
| Urethrostomy | 1 |
| Renal transplant | 1 |
| Nephrolithotomy | 1 |
| Bladder diverticulum | 1 |
| Total | 19 |

Sixty seven patients were pleased with clean intermittent catheterisation. Control of incontinence increased their self confidence, enabling them to participate in a wider range of activities. Four found it just satisfactory, and three thought it unsatisfactory but still preferred to continue with it rather than wear 'a bag'. It was abandoned in 11 patients: in two for upper tract deterioration, and five because of poor control of incontinence. Three, with good control of incontinence, did not like catheterisation, and preferred an appliance or indwelling catheter. One patient after four years clean intermittent catheterisation, learned to stay dry using only bladder expression.

## Discussion

Most of the patients in this study were severely physically handicapped and many were also mentally subnormal. Some had tried various incontinence appliances but found it difficult to keep them on because of physical deformities, obesity, and orthopaedic appliances. Even those restricted to wheelchairs preferred clean intermittent catheterisation to other systems, and were pleased to be free from cumbersome appliances and bags.

There were no clear early predictors of success with clean intermittent catheterisation. Many who initially had poor control improved with time, possibly reflecting changes in bladder activity with prolonged catheterisation. We did not repeat urodynamic studies in such patients routinely, and are thus unable to verify this hypothesis from this study.

The overall rate of complications was low; in only two patients was it stopped for upper urinary tract deterioration. Though colonisation of the urinary tract by bacteria was common, symptomatic infections were rare. Similar findings of a comparatively low rate of symptomatic infection, despite a high incidence of bacteriuria, have been reported in other series.[6 9] Only one of our patients died with acute on chronic urinary tract disease.

Compliance with the technique depends on many factors. All these patients face unique complex physical, emotional, and social problems. The attitudes of the patients, their parents, and those supporting the family seemed the most important predictive factors. Many found that clean intermittent catheterisation was actively discouraged, and adequate facilities not provided even in special schools for the disabled. Thus even some who had good control of incontinence chose to abandon clean intermittent catheterisation, while some who remained wet were grateful for small improvements.

This study confirms that clean intermittent catheterisation is a useful, acceptable, and safe technique for children with neuropathic urinary incontinence. Even the severely handicapped considered better control of incontinence led to a more active, useful, and enjoyable life.

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# Postmicturition residual bladder volumes in healthy babies

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SUMMARY Thirty eight assessments of postmicturition residual volume were undertaken in 34 babies of various gestational and postnatal ages using abdominal ultrasonography. Twenty one (54%) babies had no detectable residual bladder volume. In all cases manual expression of the bladder failed to eliminate the residual volume. The formula widely used in the estimation of fetal bladder size and urine output is not applicable in the newborn infant.

Considerable residual postmicturition urine volumes have previously been reported in newborn infants.[1 2] This finding effectively invalidates any measured urine output because in the presence of an unknown residual volume such a collection does not reflect the true urine flow rate.

During a recent study on renal function, in which standard clearance methodology was used, we manually expressed the bladder after each void to ensure complete emptying. However, in every case we failed to express any urine. We therefore investigated bladder emptying in a number of healthy babies to establish the incidence of appreciable residual volumes and the value of manual expression.

A mathematical formula, first described for the calculation of fetal bladder volume and derived from bladder measurements obtained on ultrasonography, has been similarly employed in the newborn and we concurrently evaluated its application in this situation.[2]

## Subjects and methods

Abdominal ultrasonography was performed on 34 babies with parental consent; there were 20 boys and 14 girls. Their gestational ages ranged from 24 to 43 weeks and their postnatal ages from 1 to 92 days. Two sets of twins were included. Four babies were studied twice on different days.

All scans were performed using an Advanced Technology Laboratories Mark 100 ultrasonic scanning system. This is a portable, real time sector scanner with a 7·5 MHz rotating wheel transducer. The scans were obtained by a direct scanning technique and the images were recorded on a multiformat matrix.

Scans were taken before and after micturition in longitudinal and transverse planes. From these views measurements of three bladder diameters were obtained using electronic calipers: maximal longitudinal (a), transverse (b), and anteroposterior (c). The bladder volume was calculated using the formula $4/3 \times \pi \times a/2 \times b/2 \times c/2$.[3]

Where a postmicturition residual volume was detected suprapubic pressure was applied to express the urine.

## Results

Measurements of bladder volume were obtained immediately before voiding in 29 babies and the volume voided measured in 30. Thirty eight postmicturition scans were obtained.

Bladder volumes were calculated using the formula described: the results are shown in the table.

Twenty one babies (54%) emptied their bladder completely. The remainder, seven girls and 10 boys, had a mean calculated residual volume of 1·4 ml (range 0·02–6·6 ml). Girls had larger calculated residual volumes (mean 2·4 ml) than boys (0·8 ml); $p<0·001$ by Wilcoxon rank sum test. Suprapubic pressure failed to express the residual volumes in all cases.

In 26 of the infants studied measurements for calculation of the volumes before and after micturition were obtained in addition to a measured spontaneous void. When the estimated bladder volume (premicturition volume less the residual volume) was compared with the measured voided volume, there was a positive correlation with an r value of 0·72. This relatively good correlation, however, concealed a considerable lack of agreement between the two measurements. The mean error of

Table *Details of the 34 babies (38 assessments) and calculated bladder volumes*

| *Assessment* | | *Postnatal age (days)* | *Gestational age at birth (weeks)* | *Premicturition calculated bladder volume (ml)(A)* | *Actual voided volume (ml)(B)* | *Postmicturition calculated residual volume (ml)(C)* | *Calculated voided volume (ml)(A-C)* | *Percentage error in calculated void ((A-C)-B/B)×100%* |
|---|---|---|---|---|---|---|---|---|
| *No* | *Sex* | | | | | | | |
| 1 | M | 48 | 29 | — | — | Nil | — | — |
| 2 | M | 92 | 26 | — | 13·6 | 0·10 | — | — |
| 3 | F | 23 | 34 | 8·6 | 6·6 | Nil | 8·6 | 30·3 |
| 4 | M | 34 | 30 | — | — | Nil | — | — |
| 5 | M* | 9 | 32 | 10·2 | 5·6 | 0·10 | 10·1 | 80·4 |
| 6 | M** | 9 | 32 | — | — | Nil | — | — |
| 7 | F | 7 | 32 | 6·2 | 6·3 | 0·30 | 5·9 | −6·3 |
| 8 | M | 5 | 40 | — | — | Nil | — | — |
| 9 | M* | 14 | 33 | 10·1 | — | Nil | 10·1 | — |
| 10 | M** | 14 | 33 | 13·8 | 8·2 | Nil | 13·8 | 68·3 |
| 11 | M | 5 | 36 | 5·2 | 3·5 | 0·20 | 5·0 | 42·9 |
| 12 | F | 2 | 38 | 10·7 | 8·2 | Nil | 10·7 | 30·5 |
| 13 | F*** | 2 | 37 | — | 3·4 | Nil | — | — |
| 14 | F*** | 9 | 37 | 16·2 | 15·3 | 1·50 | 14·7 | −3·9 |
| 15 | M | 9 | 36 | 15·3 | 11·4 | 0·10 | 15·2 | 33·3 |
| 16 | M | 78 | 24 | 4·7 | 3·8 | 0·02 | 4·7 | 23·2 |
| 17 | F | 5 | 37 | 10·5 | 5·7 | Nil | 10·5 | 84·2 |
| 18 | F | 5 | 41 | 16·7 | 12·9 | Nil | 16·7 | 29·5 |
| 19 | F | 1 | 37 | 15·8 | 9·0 | Nil | 15·8 | 75·6 |
| 20 | M | 3 | 37 | 28·0 | 15·6 | 0·20 | 27·8 | 78·2 |
| 21 | M | 3 | 40 | 13·4 | — | Nil | 13·4 | — |
| 22 | F | 2 | 43 | — | — | Nil | — | — |
| 23 | F | 1 | 40 | 12·5 | 16·0 | 3·00 | 9·5 | −40·6 |
| 24 | F | 1 | 37 | 6·9 | 8·5 | 0·60 | 6·3 | −25·9 |
| 25 | M | 3 | 36 | 7·0 | 6·0 | 0·10 | 6·9 | 15·0 |
| 26 | M | 4 | 36 | — | 22·0 | Nil | — | — |
| 27 | M | 4 | 36 | 12·4 | 11·0 | Nil | 12·4 | 12·7 |
| 28 | M | 15 | 27 | 3·7 | 3·9 | Nil | 3·7 | −5·1 |
| 29 | F | 2 | 37 | 12·7 | 6·0 | 0·40 | 12·3 | 105·0 |
| 30 | M | 2 | 40 | 12·9 | 7·0 | 0·70 | 12·2 | 74·3 |
| 31 | F | 3 | 38 | 19·9 | 25·0 | Nil | 19·9 | −20·4 |
| 32 | F | 2 | 36 | 15·3 | 12·5 | 4·60 | 10·7 | −14·4 |
| 33 | M | 3 | 41 | 5·6 | 8·5 | Nil | 5·6 | −34·1 |
| 34 | F**** | 74 | 24 | 9·0 | 2·0 | 4·10 | 4·9 | 145·0 |
| 35 | M | 7 | 37 | 8·6 | — | 6·60 | 2·0 | — |
| 36 | M | 7 | 40 | — | 20·5 | 0·50 | — | — |
| 37 | M | 2 | 39 | 17·1 | 19·0 | Nil | 17·1 | −10·0 |
| 38 | F**** | 81 | 24 | 6·9 | 4·8 | Nil | 6·9 | 43·8 |

Results for babies scanned twice are displayed individually and denoted by paired asterisks.

the calculated compared with actual voided volume was 31·2%; this ranged from an underestimation of 40·6% to an overestimation of 145% (fig 1). Using the paired $t$ test, the two sets of observations were significantly different ($0{\cdot}05>p>0{\cdot}02$).[4]

## Discussion

Our observations indicate that the above formula, in its present form, is not applicable in the assessment of bladder volume in newborn infants. The formula in based upon the assumption that the bladder is ovoid in shape. It was initially validated by scanning the bladder of a term stillborn infant after the intravesical instillation of known volumes of water

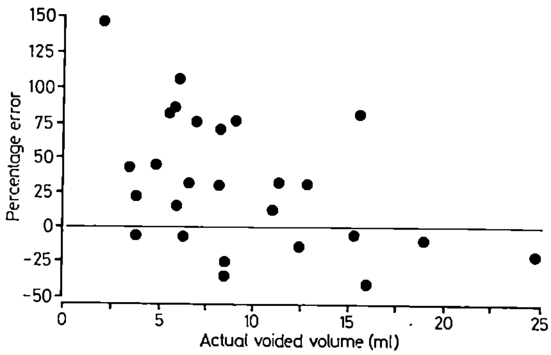

Fig 1 *Percentage error of the calculated voided volume when compared with the actual voided volume.*

over a range of 4–39 ml, and it has been used widely in the measurement of bladder size and assessment of urine flow rates in the fetus. The reported mean error, on comparison of the actual bladder volume and measurements, was 0·7 ml and it was similar over the range of volumes, indicating that the greater the bladder volume, the greater the accuracy of the method.[3] In many of our study infants the bladder on ultrasonography appeared complex in shape, particularly in girls where it was crescentic on transverse section, and the residual volumes, where seen, appeared small: these factors may explain the poor accuracy of the calculated values (fig 2 a,b,c, and d).

Nevertheless our results differ from those of Osborne *et al* who reported that 15 of 16 babies studied (94%) did not empty their bladder completely[2]; 54% of the infants studied here did.

Babies in the study of Osborne *et al* were all born at term, with an age range of 2 to 13 days, whereas our infants were of various gestational and postnatal ages. If only the babies of 37 weeks' gestation or greater are considered, however, the percentage who empty their bladder completely remains similar at 58%.

This difference may be related to the type of ultrasound machine used: Osborne and his colleagues used a static scanner and it is possible that during scanning bladder refilling was occurring as measurements were taken, resulting in a higher incidence of residual volume.

Our results also differ from those of O'Donnell

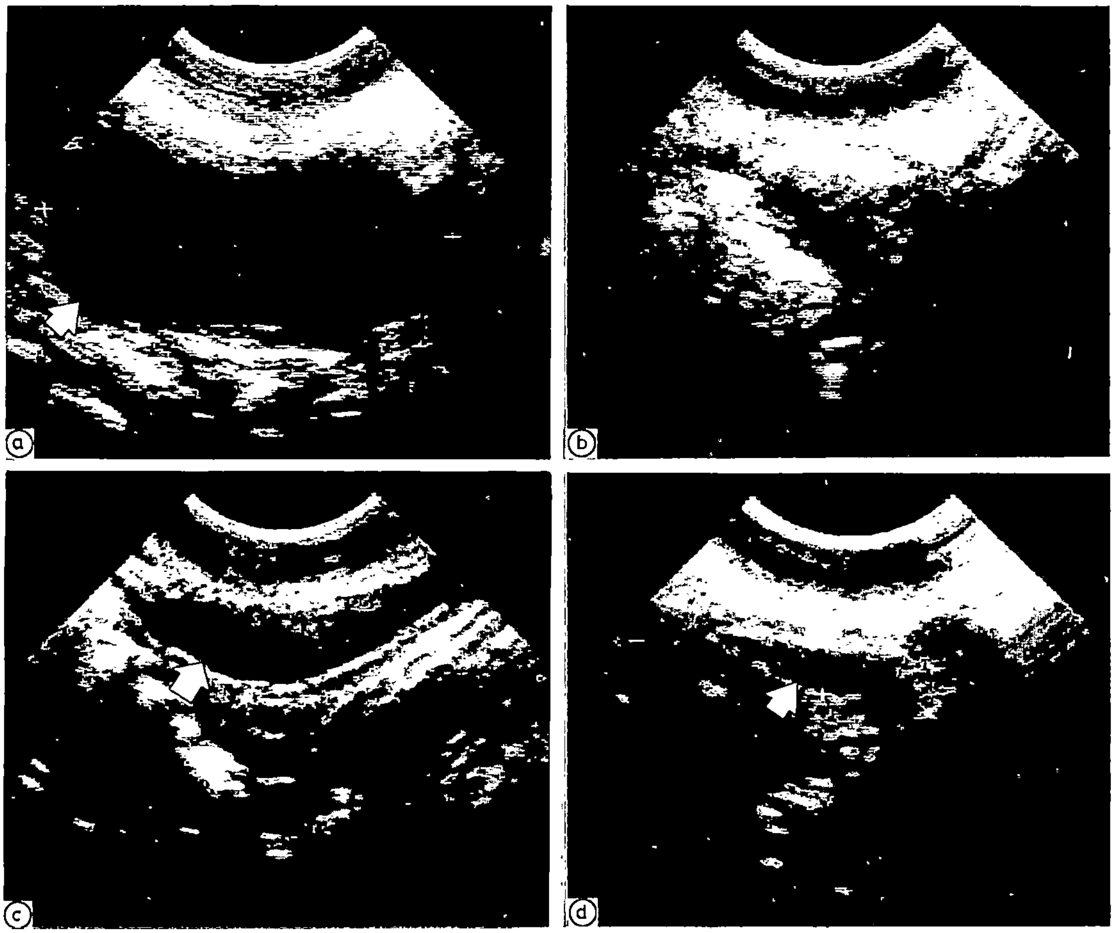

Fig 2 *Ultrasound scans of an infant boy before (a) and after (b) micturition showing a complete void. Ultrasound scans of an infant girl before (c) and after (d) micturition showing residual volume and 'crescentic' shape of bladder. (The arrows indicate bladder wall.)*

and O'Connor who reported that large residual volumes were more common in infant boys.[1]

In summary, 54% of the babies studied emptied their bladder completely. In the remainder a post-micturition volume was detected, however, in most cases this was small, and in all cases it was inexpressible.

We suggest that manual expression after micturition in the newborn is not a useful manoeuvre: it is uncomfortable for the babies and fails to eliminate any residual urine. In addition the formula for estimation of fetal bladder size is not applicable in infants.

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# Referral patterns after school medical examinations

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SUMMARY The incidence of sensory or language abnormalities and the factors influencing the clinical medical officers' decisions to refer children who failed developmental tests were studied. There were 1259 children examined and referrals for vision, hearing, and language assessment were made for 39(3·1%), 75(6·0%), and 27(2·1%), respectively. About 80% of these problems, however, were not known to the child health services when the children were 3·5 years old, mainly because children had moved to the district after the age of 3·5, and did not attend the 3·5 year screening clinics. Referrals formed only a small percentage of children who failed a test (11·0% failed vision, 19·5% hearing, and 24·6% language assessments). For vision and hearing the most important reason for the discrepancy was the clinical medical officers' wish to reassess children who failed the test before referring them. For the language test the clinical medical officer's often believed that the screening did not reflect the child's skills, which suggests that language screening as currently used in the district is not effective. Evaluation of the examination has highlighted the need to review the tests being used.

A school entry medical examination takes place in most district health authorities.[1 2] This is currently the only scheduled examination of primary school children and is a last chance to identify systematically undetected health problems that could affect the child's educational performance,[2-4] although some would support regular screening (for example, for vision) during school years.[5] It has been claimed that between 10 and 20% of children in Britain reach school with defects that should have been detected earlier.[6] There is also a suspicion that examiners who identify a preschool child who has failed a test do not always take the required action. There is, however, little factual information to support these opinions, and explanations of why this might occur have not been established.

In West Lambeth Health Authority a precoded questionnaire recording the main examination results and referral details of those children whose school entry medical assessment was unsatisfactory has been used since 1984. Information about preschool examinations has been entered on to computer. We were therefore able to check whether those sensory or physical health problems identified in the school entry examination were previously known, and if not what the possible reasons were. We also explored the reasons why clinical medical officers did not refer children for further investigations when they failed tests according to pre-established thresholds.

## Subjects and methods

Children attending the 42 primary schools covered by the West Lambeth Health Authority are routinely examined between the ages of 5·0 and 5·5 years.[7] In the school year 1985–6 the tests included in the sensory and language assessments were: corrected and uncorrected distant vision for each eye (using the Snellen chart for distant vision), examination for squint, 25 dB sweep audiometry at seven frequencies for each ear, word discrimination tests of hearing (the Stycar 12 high frequency picture test and the Stycar low frequency picture test), and picture based tests of comprehension and expressive language. Many of the tests of hearing and language used in this district are associated with the child's educational performance at age 8.[7] The sweep audiometry and distant vision assessments are undertaken by the school nurses and the other tests are done by clinical medical officers. All the tests have been standardised and all the staff have undergone inservice training.

Vision, hearing, or language defects were defined as follows: for vision, an uncorrected acuity of 6/9 or below in either eye, or corrected acuity of 6/9 or below, or definite or doubtful squint. Hearing defects were defined as failures at three or more frequencies in the sweep audiometry in either ear, or refusal or unsatisfactory response to the high or low frequency pictures in either ear. Language defects were defined as a refusal or low scores for comprehension or expressive language, or unintelligible articulation.

Children were divided into three groups on the results of this assessment: those who failed a test and were referred to a specialist; those who failed a test but were not referred to a specialist, and those who did not fail the tests yet were referred to the specialist.

In the first group we were interested to assess whether the children's sensory or language problems were known to the community health service. This was checked with the information from the 3·5 year examination stored in the district computer. Data on examinations before the age of 3·5 were not available for this cohort of children. Two other items of information were used in this analysis; clinical medical officers' assessment at the age of 5 as to the age the detected problem was likely to have been present, and whether the child was previously living in the district.

In the second group we assessed possible reasons why the child was not referred despite failing a test (table 1). The clinical medical officers were sent a form to be completed for each child. Subsequently, among the children who failed a test, we compared those who were referred and those who were not referred for each type of problem with respect to child's sex, whether the child was brought up in an English environment, which clinical medical officer carried out the examination, the severity of the sensory or language problem, and the cooperation of the child during the assessment. The degree of association was assessed using logistic regression analysis.[8]

The third group who were referred without failing a test was too small for analysis.

Table 1 *Number of children not referred for reason given despite failing vision, hearing, or language assessment*

| | *Vision* (*n*=99) | *Hearing* (*n*=178) | *Language* (*n*=280) |
|---|---|---|---|
| Screening not reflective of child's skills | 1 | 5 | 121 |
| Results doubtful—child to be recalled | 43 | 75 | 26 |
| Not severe enough to need treatment | 6 | 2 | 38 |
| Expected to improve spontaneously | 0 | 10 | 24 |
| Already under clinical supervision | 16 | 14 | 10 |
| Parent not present or refuse referral | 2 | 7 | 1 |
| Findings recorded wrongly | 5 | 5 | 2 |
| Child referred but not recorded on form | 7 | 24 | 7 |
| Child moved to another school | 17 | 31 | 37 |
| Other reason | 2 | 5 | 14 |

## Results

In 1985–6 a precoded form was completed for 1259 (69%) of the 1825 eligible children. Of the children examined, 141 (11·2%) were referred to a specialist, 571 (45·4%) failed a relevant test and were not referred, and 22 (1·7%) were referred despite no failure being recorded.

### AWARENESS OF SENSORY OR LANGUAGE PROBLEMS

The figure shows the distribution of children referred for ophthalmic, audiological, or language assessment according to whether they had been living in the district, whether they had been seen at the age of 3·5, and whether a problem had been identified at that time. Between a quarter and a third of these children did not live within the district health authority's area, and another third were not seen at the age of 3·5. Most of those seen had a previously identified problem. This was particularly the case for children referred for speech therapy.

### FACTORS AFFECTING THE REFERRAL PATTERN

Table 1 shows the reasons why children who had failed a vision, hearing, or language test were not referred. The main reasons were that the screening did not reflect the child's skill, or the results were doubtful. Eighty five children had moved to another school so the follow up form could not be completed. Clinical medical officers often decided to recall children who failed vision, hearing, and language tests before deciding whether referral was necessary. Only for the language screening test, however, did they decide not to refer because they considered their findings did not reflect the child's real ability. Many children who failed the language test were not considered disabled enough for referral, or were expected to improve spontaneously.

In the analysis comparing the characteristics of those children who were referred and those who were not referred, those who were referred but for whom this fact was not recorded in the form were combined with those who had been referred, but those already receiving treatment were excluded

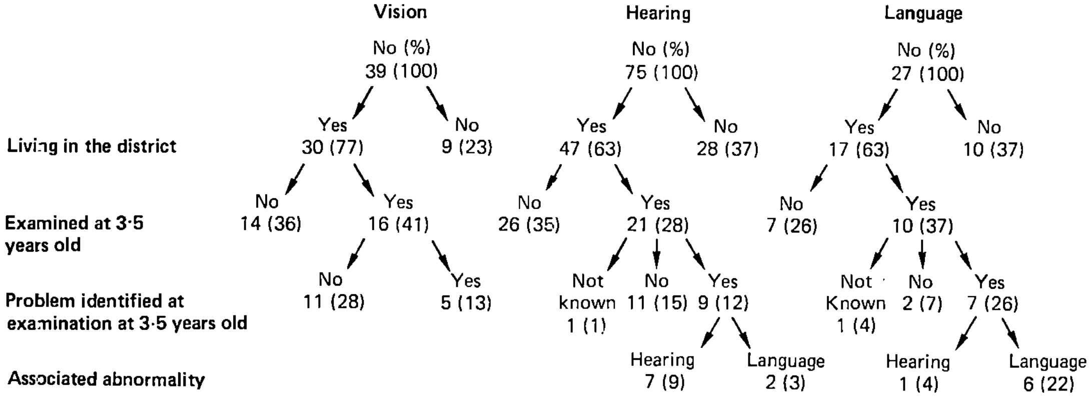

Figure *Background information about children referred to a specialist because of a defect in vision, hearing, or language comprehension.*

from the analysis (table 1). The small number of children who were referred whose test results were wrongly recorded as failures were included among those who were not referred. This group was not large enough to influence the results either way. Table 2 shows the percentages and 95% confidence intervals of probability of referral for speech therapy, or audiological and ophthalmic assessment. No significant differences were found regarding sex of the children, language spoken at home, and children's cooperation (but there were too few uncooperative children for analysis). The number of tests failed (a proxy measure of severity) was highly significantly associated with the probability of being referred for audiological assessment ($p<0{\cdot}001$) and for ophthalmic assessment ($p<0{\cdot}05$). There was a trend with number of problems in the probability of referral to speech therapy but this was not significant. Significantly fewer children were referred who failed only the comprehension language test compared with those who failed the expressive language test, or both tests (18·4% and 39·9%, respectively). There were significant differences among examiners in their referral pattern to the three specialists. Some clinical medical officers consistently referred few children, others consistently referred a lot, and others referred proportionately more children with one type of abnormality than another.

Table 2 *Probability of being referred if failing a test according to English environment, sex, number of failed assessments, and child's cooperation*

| | *Ophthalmology* | | *Audiology* | | *Speech therapy* | |
|---|---|---|---|---|---|---|
| | *Total No* | *% Referred (2 SE)** | *Total No* | *% Referred (2 SE)** | *Total No* | *% Referred (2 SE)** |
| English environment: | | | | | | |
| Yes | 80 | 52·5 (10·9) | 183 | 50·2 (7·2) | 186 | 30·1 (6·5) |
| No | 46 | 56·5 (14·3) | 55 | 43·6 (13·1) | 111 | 32·4 (8·7) |
| Sex: | | | | | | |
| Boys | 69 | 56·5 (11·7) | 124 | 45·2 (8·8) | 157 | 33·8 (7·4) |
| Girls | 59 | 50·9 (12·8) | 114 | 52·6 (9·2) | 140 | 27·9 (7·4) |
| No of problems: | | | | | | |
| 1 | 56 | 41·0 (12·9) | 107 | 31·8 (8·8) | 221 | 28·5 (6·0) |
| 2 | 68 | 64·7 (11·4) | 93 | 52·7 (10·1) | 49 | 34·7 (13·3) |
| 3 | 2† | | 38 | 86·8 (10·8) | 27 | 44·4 (18·7) |
| Child's cooperation: | | | | | | |
| Satisfactory | 122 | 53·3 (8·9) | 224 | 47·8 (6·5) | 271 | 29·9 (5·5) |
| Unsatisfactory | 4† | | 14 | 64·2 (25·1) | 26 | 42·3 (17·3) |

†Confidence interval not calculated for groups of less than 10 children.
*% Referred (2 SE) gives limits for 95% confidence interval.

## Discussion

The results of this study highlight the two main reasons for a child not having been previously found to have a sensory or language problem: the high percentage of children who only recently moved to the district, and the large percentage of children who were not examined at the age of 3·5.[9] These two reasons explain about 66% of the undetected cases. Of those with a problem who were seen at the age of 3·5 years, half were first detected at that stage. A more specific problem concerning hearing is that hearing defects are often intermittent. For some of the newly detected children referred at the age of 5 the sensory problem may therefore be a new problem.

For the examination of vision the comparatively large percentage of children who were not identified as having a problem earlier may have been due less to the progressive nature of the disorder than to the recognised low sensitivity of the Stycar 5 letter test used at the age of 3·5 years.[10] In this district there is a commitment to change the assessment test at the age of 3·5. This may become possible now that the Sonksen-Silver acuity letter match screening pack is available, which is a multiletter system.

Regarding language examination there were remarkably few children referred with a current language problem who were not identified as having the disorder at the age of 3.5.

These results indicate that the families with young children who change address frequently pose a serious problem to an effective developmental screening programme in inner city areas in London. As it is known that most movers change address between neighbouring health authorities, the only possible way to keep track of these children would be through collaborative arrangements between authorities. This should include a commonly designed form with a clear summary to ensure that the personnel in each district become acquainted with their health needs.

Non-attendance for routine examinations tends to increase with age, and reflects the fact that a large percentage of parents of older children simply do not use these services. Health visiting would be the only way of reaching such children.

The proportion of children in the district failing tests according to the established norms was extremely high (56·7%). Figures obtained from the national child development studies (1958 cohort) on 7 year old children showed approximately 8%, 6%, and 10–13% had defects in vision, hearing, and speech respectively, and speech problems increased two or three fold in social classes IV and V.[11–13] In Lambeth, with a high incidence of social deprivation, and wide ethnic mix, the high rate of problems was not unexpected. In deciding whether a child should be referred, clinical medical officers seemed to be influenced by severity, measured by the number of failed tests. For language problems, however, undetected factors may have had an important influence on the examiners.

This study also indicates that language assessment at school medical examination needs a rigorous review, as only one in nine children who failed a test was referred and these children were only slightly less delayed than those who were not referred. There are insufficient speech therapists available in the district to cope with all 5 year old children who fail a test, and indeed it would be unwise to refer such a large number of children without a careful assessment of such a policy. Unfortunately few studies evaluating the usefulness of speech therapy seem to be available, despite the many methods available.[14] There seem to be two options: if speech therapy were only effective when directed at individual children then school medical examinations should only aim to detect a small percentage (say 5%) of children with severe speech problems. Alternatively if 'speech therapy' could be practiced on groups of children or speech therapists were able to train an intermediate group for more intensive treatment (for example, the children's parents or class teachers) then tests to identify the higher percentage of children with language delay would be justified. Any intervention should be shown to be effective in enabling the child to make better use of communication skills and educational opportunities. The number of children detected by any screening method should match the resources available for treating them.

In conclusion, this study shows that a large number of children with sensory or language defects were unknown to the community health services, mainly because a large number of these children were newcomers to the district, or did not attend the medical examination at the age of 3·5 years. The current tests to identify children with language delay are of limited help in deciding who should be referred, and they are currently being revised.

We thank everybody concerned with the school entry examination in the West Lambeth Health Authority, Professor W W Holland for his encouragement, Miss S Mandalia for her help and Mrs A Childs for her secretarial help. The study was supported by grants from the South East Thames Regional Health Authority and the DHSS.

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# Randomised controlled trial of two methods of weaning from high frequency positive pressure ventilation

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SUMMARY Forty preterm infants suffering from respiratory distress syndrome were entered into a randomised controlled trial to assess the importance of the length of inspiratory time during weaning from high frequency positive pressure ventilation (HFPPV). Two weaning regimes were compared: in one (group A) inspiratory time was limited to 0·5 seconds throughout weaning, in the other (group B) ventilator rate was reduced by increasing both inspiratory and expiratory time (inspiration:expiration ratio constant) until inspiratory time reached 1·0 seconds. At ventilator rates of 20 and 40 breaths/minute an acute comparison was made in all 40 infants of the two inspiratory times; despite the lower mean airway pressure associated with the shorter inspiratory time blood gases were maintained. There was no difference in the incidence of pneumothoraces or need for reventilation between the two regimes but infants in group A had a shorter duration of weaning. We conclude limitation of inspiratory time to 0·5 seconds during weaning from HFPPV is advantageous to preterm infants with respiratory distress syndrome.

High frequency positive pressure ventilation (HFPPV), defined as rates of 60 breaths/minute or greater, has recently been used for preterm neonates with great success.[1] HFPPV has been associated with a reduction in the incidence of pneumothoraces, both in trials involving retrospective or non-randomised controls[2-4] and more recently in a multicentre randomised controlled trial.[5] Physiological studies have shown that fast rates reduce active expiration,[6 7] a respiratory interaction that precedes the development of pneumothoraces,[8] thus supporting the clinical findings.[2-5] In the acute stage of respiratory distress syndrome, the infants' spontaneous respiratory rates are inversely proportional to their gestational ages.[9] Thus when fast rates are used for very immature infants, synchronous respiration is induced and oxygenation improved.[10]

At fast rates, inspiratory time is necessarily reduced. This limitation of inspiratory time may be one explanation for the success of HFPPV, as prolongation of inspiratory time certainly has been shown to increase both the incidence of pneumothoraces[11] and of active expiration.[12] In a recent short term study we found that limiting the inspiratory time to 0·5 seconds during the weaning process from HFPPV was also advantageous.[13] It was associated with a reduction in active expiration and a significant increase in minute volume when compared with the effects of a longer inspiratory time.[13] Weaning from HFPPV, however, is only initiated during recovery from respiratory distress syndrome, and during this phase the lungs become more compliant resulting in an increased time constant of the respiratory system.[14] A tenable argument, therefore, would be that during weaning the inspiratory time should be prolonged as the rate is reduced in order to ensure maximum inflation and oxygenation and thus prevent the development of atelectasis. The aim of this study was to investigate, by means of a randomised controlled trial, if the length of inspiratory time was an important determinant of the duration of weaning from HFPPV.

## Patients and methods

### METHODS

Infants were eligible for inclusion in the study, if suffering from respiratory distress syndrome and ventilated at rates in excess of 60 breaths/minute. In all instances we had followed our usual weaning protocol, in which both rate and peak inspiratory pressure were reduced until a ventilator rate of 60 breaths/minute and a peak inspiratory pressure of 20 cm $H_2O$ were reached.

Subsequently weaning from ventilation was attempted solely by reducing the rate while peak inspiratory pressure was held constant. When the ventilator rate reached 20 breaths/minute aminophylline or theophylline were administered either intravenously or orally.[15] At ventilator rates of 60 breaths/minute infants were entered into the study and randomised to weaning groups A or B: in group A the ventilator rate was reduced by increasing expiratory time only, inspiratory time was held constant at 0·5 seconds; in group B the ventilator rate was reduced by increasing both inspiratory and expiratory time (the inspiration: expiration ratio being held constant at 1:1·2) until the inspiratory time reached 1·0 seconds. Subsequently the rate was reduced by increasing the expiratory time only. In every other respect the protocol for weaning from ventilation was similar in both groups, in particular the criteria used for altering ventilator rate and reintubation.

All changes in ventilator settings were made by the clinical team caring for the infants. Throughout weaning, the infants' oxygen pressure was continuously monitored, either by a transcutaneous electrode or a Searle intra-arterial electrode. During weaning blood gases were measured as clinically indicated and routinely every four hours. Ventilator rate was reduced only if either the infant had developed a respiratory alkalosis or the blood gases had been maintained over the four hour period. The inspired oxygen concentration was reduced if the arterial oxygen pressure exceeded 7·3 kPa, regardless of whether a reduction in ventilator rate was made. After a change in ventilation the arterial blood gases were checked within 40 minutes, and further ventilator rate reduction made if the infant had a persisting respiratory alkalosis. Ventilator rate reduction was made in steps of '5 breaths/minute', until the infant was receiving endotracheal continuous positive airways pressure (CPAP). Arterial blood gases were checked after the infant had been receiving CPAP for one hour and if there was no evidence of a respiratory acidosis (pH <7·25) the infant was then extubated.

Mean airway pressure is related to the length of inspiratory time,[16] and when related to ventilator rate it differed between the two regimes (fig 1). To compare the two regimes, therefore, two separate comparisons were made:

*(1) Comparison of the short term effects of changes in inspiratory time*

All infants at ventilator rates of 40 and 20 breaths/minute were studied at the inspiratory time of both regimes for 30 minute periods; the inspired oxygen concentration was held constant during this comparison. At the end of each 30 minute period arterial oxygen and carbon dioxide pressures, pH, and base deficit were compared. After this one hour period study the infant was then returned to the original randomised regime.

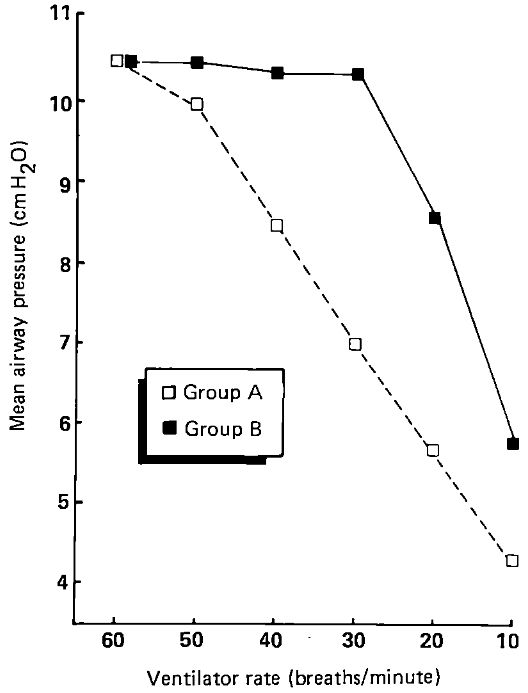

Fig 1 *Mean airway pressure during weaning associated with the limited inspiratory time (group A) compared with the longer inspiratory time (group B) related to ventilator rate.*

*(2) Comparisons of the longer term effects of changes in inspiratory time*

The duration of weaning, the number of pneumothoraces and need for reventilation were compared between the infants randomised to the two regimes. The duration of weaning was defined as the time from entering the study until first extubation. Reventilation was any episode of reintubation and ventilation after first extubation.

TRIAL SIZE

Using results derived from 20 infants previously ventilated on our unit we calculated that a trial population of 40 infants was necessary to detect with 85% power at the 5% level a significant difference of 24 hours in the duration of weaning between the two groups.

### STATISTICAL ANALYSIS

To determine if differences between the two groups and inspiratory times were significant either a Fisher's exact test or Wilcoxon rank sum test was used.

### PATIENTS

Twenty patients were randomised to both groups A and B. All the patients were suffering from respiratory distress syndrome, as evidenced by the development of respiratory symptoms within four hours of birth that persisted for longer than 24 hours, initially in the absence of infection. The infants' chest radiographs showed a symmetrical reticulogranular pattern and an air-bronchogram. The infants were ventilated by oroendotracheal tubes using a continuous flow, variable pressure ventilator (Sechrist). There was no significant difference in the gestational age, postnatal age, or sex distribution between the two groups (table 1). Neither was there a significant difference in the number of infants in each group who, before weaning, had developed pneumothorax, patent ductus arteriosus, or pneumonia. Pneumonia was characterised by asymmetrical consolidation on the chest radiograph and isolation of bacteria from a tracheal aspirate in a previously non-infected infant.

Table 1 *Clinical details of patients at trial entry. Results are mean (range)*

| | *Group A* | *Group B* |
|---|---|---|
| Gestational age (weeks) | 28·5 (24–32) | 28·0 (24–32) |
| Postnatal age (days) | 4·1 (2–14) | 3·9 (1–11) |
| Males | 11 | 15 |
| Before weaning: | | |
| Pneumothoraces | 2 | 1 |
| Patent ductus arterious | 5 | 4 |
| Pneumonia | 3 | 4 |

One infant, a girl of 24 weeks' gestation, randomised to group A, developed necrotising enterocolitis during the weaning process and died. The results of the 39 infants who completed the trial are presented.

Ethical permission for this study was granted by the King's College ethics committee.

## Results

At neither ventilator rates of 20 nor 40 breaths/minute were arterial blood gases significantly different at the inspiratory times of the two regimes (table 2).

The duration of weaning was significantly shorter in group A than group B. The mean duration was 110 hours (range 11–485) in group A and 224 hours (range 14–864) in group B ($p<0·01$) (fig 2). Only two infants developed pneumothoraces during the weaning process, both of these infants were in group B, and two infants from each group developed a patent ductus arteriosus during the weaning process; all responded to medical management. There was no significant difference in the number of infants who required reventilation in the two groups: there were four in group A and eight in group B.

## Discussion

In the acute comparison, despite a lower mean airway pressure when related to ventilator rate,

Table 2 *Arterial blood gases and inspired oxygen concentrations at two inspiratory times at 40 and 20 breaths/minute. Results are mean (range)*

| | *Ventilator rate 40 breaths/minute* | | | | *Ventilator rate 20 breaths/minute* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Group A* | | *Group B* | | *Group A* | | *Group B* | |
| Time (seconds) | 0·5 | 0·7 | 0·7 | 0·5 | 0·5 | 1·0 | 1·0 | 0·5 |
| Arterial oxygen pressure (kPa) | 8·7<br>(6·4–9·7) | 8·4<br>(7·2–10·0) | 8·0<br>(5·2–9·3) | 8·3<br>(6·4–14·6) | 8·9<br>(7·6–10·9) | 8·6<br>(7·6–10·4) | 9·1<br>(7·2–11·5) | 8·7<br>(7·5–14·4) |
| Arterial carbon dioxide pressure (kPa) | 5·3<br>(3·9–6·3) | 4·9<br>(4·4–6·0) | 5·6<br>(3·9–6·7) | 5·2<br>(4–6·3) | 5·2<br>(4·4–6·7) | 4·8<br>(3·7–5·7) | 5·6<br>(3·9–7·2) | 5·6<br>(3·5–6·5) |
| pH | 7·32<br>(7·27–7·46) | 7·33<br>(7·23–7·40) | 7·34<br>(7·28–7·40) | 7·31<br>(7·23–7·35) | 7·32<br>(7·25–7·42) | 7·34<br>(7·30–7·40) | 7·33<br>(7·25–7·40) | 7·33<br>(7·28–7·39) |
| Base deficit | 4·8<br>(1·2–8·5) | 5·3<br>(0·1–7·9) | 4·6<br>(1·6–12·6) | 6·6<br>(2·1–8·5) | 5·6<br>(3·2–7·5) | 4·9<br>(0·8–8·5) | 6·0<br>(2·3–11·5) | 5·4<br>(1·1–12·0) |
| Fractional inspiratory oxygen (%) | 42 (23–60) | | 38 (25–55) | | 31 (21–40) | | 28 (21–45) | |

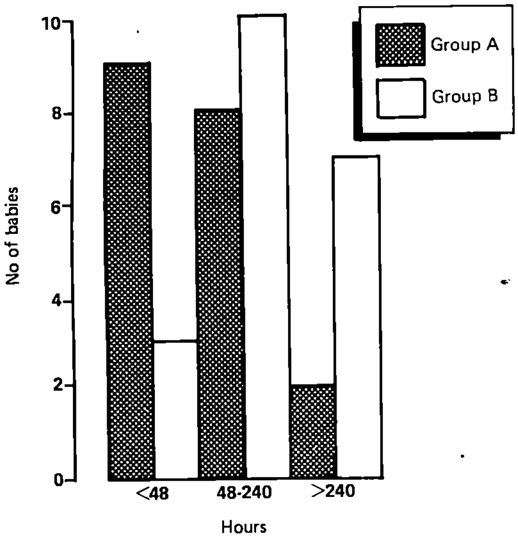

Fig 2 *The number of infants in groups A and B extubated in each of three time periods.*

oxygenation was maintained at the shorter inspiratory time. Mean airway pressure has previously been shown to be an important determinant of oxygenation.[16] That study, however, included ventilated and paralysed infants, and among infants capable of making appreciable, spontaneous respiratory effort mean airway pressure is unlikely to be the only determinant of oxygenation. In our short term weaning study we found that limiting the inspiratory time resulted in an increase in minute volume and a reduction in active expiration; both of these factors would tend to improve oxygenation.[9]

During this study only two infants developed a pneumothorax, both in group B. This pneumothorax rate is perhaps surprisingly low as we would predict, using the results of our short term study,[13] that the infants in group B would all be expiring actively, and hence at risk of developing an airleak.[17] We have, however, only shown a significant association with pneumothorax when active expiration is seen during the acute stage of respiratory illness, in infants who are being 'fully' ventilated.[8 17] The present results suggest that infants, with more compliant lungs being ventilated at a reduced rate, even when actively expiring, may not be at risk of developing an air leak.

In group A a smaller number of infants required to be reintubated thus suggesting that the limited inspiratory time was sufficiently long to prevent the development of atelectasis during weaning. During ventilation expiratory time must be long enough to allow complete lung deflation, particularly at fast rates.[4] In both groups, as ventilator rate was reduced, the expiratory time was longer than the inspiratory time. Although in group B the expiratory time, at each ventilator rate, was shorter than in group A, there was no difference in carbon dioxide concentrations during the acute comparison, suggesting the expiratory time was adequate in both groups.

Although this study was randomised it was not possible to 'blind' the clinicians as they could determine from the ventilator settings the randomisation group of the infant. During the months in which the study was carried out, a number of doctors were involved, it seems unlikely that all were biased to one particular regime. All infants entered into the study followed our routine weaning policy, which, as described earlier, clearly instructs the method of ventilator rate reduction expected, this again reduces the possibility of bias.

We have shown a reduced frequency of reintubation and a shorter duration of weaning amongst infants in group A. These results confirm that limitation of inspiratory time during weaning is advantageous to preterm infants.

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# Motor skills in extremely low birthweight children at the age of 6 years

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SUMMARY Fifty three children aged 6 years old who had weighed less than 1251 g at birth without cerebral palsy and receiving mainstream education, were entered into a controlled study of motor skills. The index and control children were matched by age, sex, and school. The index group were considered by their teachers to have similar academic performances to their controls, although two index cases were receiving remedial teaching. On the test of motor impairment extremely low birthweight children had significantly more motor difficulties than controls. In addition, the index group had more minor neurological signs, lower intelligence quotients, and more adverse behavioural traits. The higher motor impairment scores among index children were independent of differences in intelligence quotient between the two groups. There was no association between impairment score and the presence or degree of periventricular haemorrhage or periventricular leucomalacia on neonatal cerebral ultrasound. Children with Apgar scores at five minutes of less than 7 had significantly higher impairment scores compared with those whose scores were 7 or more. Three perinatal factors (Apgar score at five minutes, neonatal septicaemia, and abnormal movements) explained 32% of the variance in impairment score at the age of 6 years. In children who do not have cerebral palsy perinatal factors may still be important in the development of motor skills. The presence of subtle neuromotor impairments at 6 years of age has implications for schooling that need further evaluation.

During the past decade improved neonatal survival has extended to the smaller low birthweight babies: those weighing less than 1251 g. Despite an appreciable incidence of major neurodevelopment impairments,[1] most survivors are free of such problems. As yet the long term outcome for the healthy survivors has not been fully evaluated. Although reports of outcome of very low birthweight children born in the 1950s[2 3] and 1960s[4] suggested a high incidence of mental retardation and educational problems, more recent reports suggest that most survivors without major impairment are coping at school.[5]

Adverse perinatal events are important in the production of later serious impairments such as cerebral palsy, or deafness, even though in many cases the exact cause remains obscure. Among preterm children the presence of changes on cerebral ultrasound scans has been correlated with later cerebral palsy.[6] Not all children with abnormal findings, however, go on to develop major impairments. This may be related to the site or extent of the brain injury, or to current methods of assessment.

We became concerned that many of our 3–5 year old survivors seemed rather clumsy on testing, and that this seemed to be independent of their developmental performance, which was normal. Such motor impairment (among children of less than 1001 g birthweight born between 1960 and 1972) has previously been noted by Nickel *et al*,[4] but in association with poor performance in intelligence tests.

We report a controlled investigation of the neuromotor performance of a cohort of children weighing less than 1251 g at birth to study the hypotheses that extremely low birthweight children have a disproportionate impairment of motor skills when compared to a matched group of children born at full term and that this impairment is related to adverse perinatal events.

## Patients and methods

Between January 1980 and June 1981, 76 children who weighed less than 1251 g at birth were discharged from the Mersey Regional Neonatal Intensive Care Unit at Liverpool Maternity Hospital. At the age of 6 years children were entered into the study if they attended normal school. Four children had died, and 14 with major impairments had been placed in special schools. Of the 58 remaining children, the parents of three declined our offer of assessment. Fifty five children (95%) were therefore entered into the study.

For each index child a classmate was selected as a control. The head teacher concerned was asked to select from the school register the child of the same sex as the index child who had the nearest birthday. Permission was obtained from the school authorities and the parents of and both index and control children before proceeding.

Each index/control pair was seen at school during the same half day visit, with one exception: one child normally resident abroad was seen at hospital and a control, of similar socioeconomic class, was selected from a local school. Parents were not present during the testing session. The examination comprised: the test of motor impairment, a formal neurological examination, and the Wechsler preschool and primary scales of intelligence (WPPSI).[7] Subsequently the parents and teachers completed behavioural questionnaires and a full medical and social history was taken. The test of motor impairment (Henderson revision, 1984)[8] comprises eight items (table 1), which are scored from standards as 0, 1, or 2. The composite score is termed the impairment score, scored from 0 (not impaired) to 16 (severely impaired). The test includes three groups of items: three tests of manual dexterity, two tests of ball skills, and three tests of dynamic balance. It has recently been extensively revised and standardised on large groups of both British and North American children.

In addition to a standard neurological examination, the following minor neurological signs, as described by Touwen,[9] were sought: dysdiadochokinesia; finger following, circling, opposition, and placing; the finger nose test; dyskinetic movements and, during heel walking, associated hand movements. Mirror movements and associated movements were also recorded according to the method of Fog and Fog.[10]

Behavioural characteristics were evaluated with a 10 item questionnaire.[11] The parent or teacher was asked to say whether the children were irritable, overactive, difficult to handle, easily frightened, shy, anxious, headstrong, clumsy, fidgety, and how often they had temper tantrums. Answers for each item were graded as the same, more, or less than other children.

Two children were found to have cerebral palsy, both with spastic hemiplegia. One of these had a severe disability, an impairment score of 16, and serious difficulties in the classroom. The other was only moderately impaired, with an impairment score of 13, and managing well at school. In view of their

Table 1 *Test of motor impairment: combined and individual scores shown as median (interquartile range)*

| | *Extremely low birthweight group (n=53)* | *Control group (n=53)* | *p Value** |
|---|---|---|---|
| **Combined scores:** | | | |
| Manual dexterity | 2.5 (1·5–3·5) | 1.5 (0·5–2·5) | 0·001 |
| Ball skills | 2·0 (0–3) | 1·0 (0–1) | 0·008 |
| Dynamic balance | 1·5 (0·5–3·75) | 0·0 (0–1) | 0·001 |
| **Individual tests:** | | | |
| Posting coins: | | | |
| With dominant hand (secs) | 21 (18·5–21·5) | 19 (17·5–20·5) | 0·004 |
| With other hand (secs) | 22 (20–24) | 21 (19–23) | 0·013 |
| Thread 12 cubes (secs) | 64 (53–81.5) | 55 (47·5–65.5) | 0·008 |
| Flower trail (No of errors) | 3 (2–5·5) | 2 (0–4·5) | 0·05 |
| Catches (out of 10) | 8 (5–9) | 9 (8–10) | 0·007 |
| Goals (out of 10) | 7 (5–8) | 8 (7–10) | 0·001 |
| Stand on dominant leg (secs) | 15 (8–15) | 15 (15–15) | 0·003 |
| Stand on other leg (secs) | 9 (5–15) | 15 (10–15) | 0·003 |
| Toe walking (out of 15) | 12 (7·5–15) | 15 (15–15) | <0·001 |
| Jump cord: | | | |
| Pass at knee height | 42 | 49 | 0·1197 |
| Pass at lower height | 6 | 3 | |
| Fail | 5 | 1 | |
| Total score | 6·0 (4·0–8·75) | 3·0 (1·5–4·5) | <0·001 |

*Mann-Whitney U test.

overt motor problems they have been excluded, with their controls, from the subsequent analysis.

All children were scanned routinely in the newborn period using an ATL 805A scanner with a 5MHz probe. Cerebral ultrasound scan findings were reviewed from still photographs without knowledge of findings at the age of 6 years. Perinatal events were abstracted from clinical records. Appropriateness of birth weight for gestational age was assessed by computing a standard deviation score, using the standards of Keen and Pearse.[12] This was then analysed both as a continuous and dichotomous variable by choosing different cut off points.

The data was coded for computer analysis by the Statistical Package for the Social Sciences (SPSSx) software package. The significance of the various comparisons was tested using non-parametric tests: the Mann-Whitney U test, the Kruskal-Wallis one way analysis of variance, the $\chi^2$ test, and Spearman's rank correlation test, as appropriate. Multiple regression was carried out using the SPSSx regression option selecting a 'F' value for entry of 0·1 and the model selected with the least standard error.

## Results

### DEMOGRAPHIC DETAILS

All control subjects were born at full term and, with one exception, were of appropriate weight for gestational age. No significant neonatal problems were reported by their mothers. Their median birth weight was 3760 g (range 2350–4760). Of the index group, 21 weighed less than 1000 g, 42 were of less than 30 weeks' gestation, and seven were small for gestational age (less than two standard deviations below the mean). The age distribution of the two samples was well matched. There was no significant difference between the two populations in social groupings and home ownership (table 2). Similar proportions lived with their natural parents, or had single mothers, and the maternal age distribution was similar. Significantly more index children were only children (p=0·001) and they tended to be older members of smaller sibships. The control group, however, had spent an average of three months more in school (p=0·037), although this difference disappeared when the total time spent in full time nursery and school education was considered.

Each class teacher was asked to grade each child's ability into one of three categories. There were no significant differences in the proportions of index or control children who were in above and below average groups, although 15 index children (28%), including two in remedial classes, were felt to be below average compared with only eight control subjects (15%), and only nine index children were performing in the above average category compared with 16 control subjects.

### TEST OF MOTOR IMPAIRMENT

In contrast to their classroom performance, the extremely low birthweight children were considerably more impaired than their matched controls. The median (range) for the index group was 6·0 (0·0–15·5) compared with 3·0 (0·0–13·0) for controls (table 1). On seven of the eight individual items of the test the extremely low birthweight group performed significantly less well than the control subjects (table 1). Despite a large overlap of results only 10 extremely low birthweight children had equal or lower scores than their matched control (figure).

### WECHSLER PRESCHOOL AND PRIMARY SCALES

The extremely low birthweight children had signifi-

Table 2 *Demographic details of index and control groups*

| | *Extremely low birthweight group (n=53)* | *Control group (n=53)* |
|---|---|---|
| Median (range) birth weight | 1050 (620–1250) | 3760 (2350–4760) |
| Median (range) gestation (weeks) | 28·5 (24–35) | 40 |
| No of boys | 33 | 33 |
| Median (interquartile range) age (months) | 73 (72–75) | 73 (72–72·5) |
| Socioeconomic class: | | |
| I and II | 12 | 13 |
| III | 17 | 23 |
| IV, V or unemployed | 19 | 14 |
| No with single mothers | 5 | 3 |
| Housing: | | |
| Council, rented | 22 | 14 |
| Private, rented | 4 | 7 |
| Private, owned | 27 | 32 |
| Both natural parents at home | 38 | 44 |
| No of siblings: | | |
| None | 17* | 2* |
| 1 | 16 | 29 |
| 2 | 15 | 12 |
| 3 | 4 | 8 |
| 4 | 0 | 0 |
| 5 | 1 | 2 |
| Rank in sibship: | | |
| One | 12 | 18 |
| Two | 14 | 20 |
| Three | 7 | 8 |
| More than three | 3 | 5 |
| Median (interquartile range) full time nursery and school attendance (months) | 36 (24–40) | 35 (24–40) |

*p<0·001, df=5, $\chi=^2$ test.

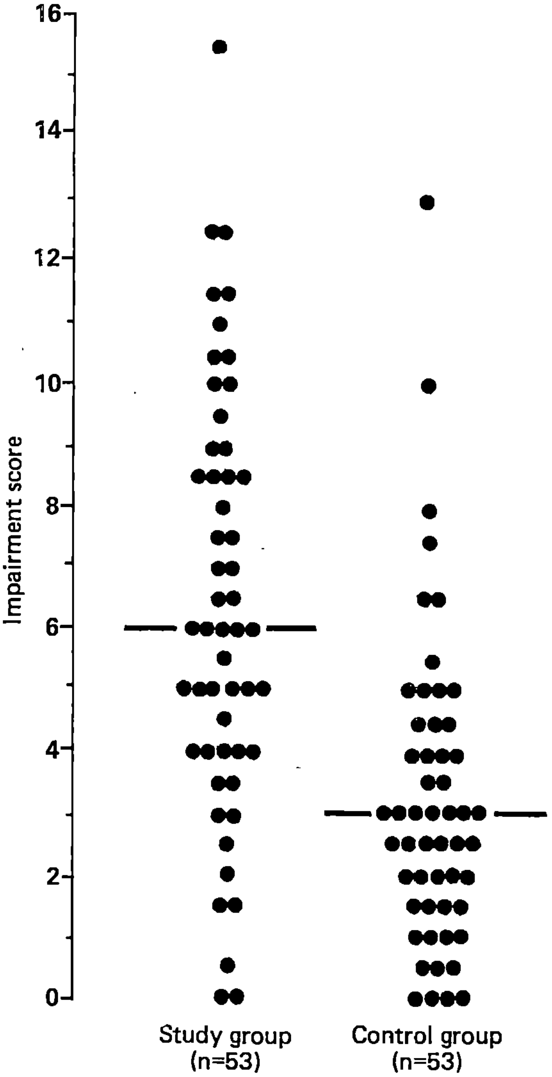

Figure *Distribution of impairment scores in study and control groups. The horizontal bar indicates the median.*

cantly lower intelligence quotients than control subjects, there being an eight point difference in median scores between index and controls (table 3). These differences persisted when both the verbal and performance aspects of the test were considered. The discrepancy between verbal and performance scores, which might be expected to indicate motor impairment, did not vary significantly between groups, indicating that the index group had an overall reduction in scores compared with control subjects.

Table 3 *Results of intelligence testing. Values are shown as medians (interquartile ranges)*

| | *Extremely low birthweight group (n=53)* | *Control group (n=53)* | *p Value** |
|---|---|---|---|
| **Intelligence quotient:** | 109 (100–119) | 117 (109–128) | 0·001 |
| Range | 82–139 | 84–139 | |
| **Verbal quotient:** | 112 (102·5–124) | 117 (109·5–131) | 0·05 |
| Information | 15 (13–17) | 16 (14–18) | 0·04 |
| Vocabulary | 28 (24–32·5) | 31 (26–34) | 0·11 |
| Arithmetic | 13 (12–15) | 14 (13–16) | 0·005 |
| Similarities | 15 (11–18) | 16 (12·5–19) | 0·07 |
| Comparisons | 21 (17–24) | 21 (20–26) | 0·15 |
| **Performance quotient:** | 100 (93–107·5) | 111 (103·5–119) | <0·001 |
| Animal house | 112 (90·5–131) | 105 (74–123) | 0·06 |
| Picture completion | 15 (12–16·5) | 16 (13–18) | 0·005 |
| Mazes | 16 (12–18·5) | 20 (16–23) | <0·001 |
| Geometric design | 12 (9–16·5) | 18 (15–21) | <0·001 |
| Block design | 15 (11–16·5) | 15 (14–17) | |
| Verbal/performance discrepancy | +11 (4·5–23) | +9 (−0·5 to 16·5) | 0·7 |
| Range | −30 to +36 | −16 to +31 | |

*Mann-Whitney U test.

The extremely low birthweight children performed significantly less well than controls on five of the 10 subscales of the WPPSI: two verbal subscales (information and arithmetic) and three performance items (picture completion, mazes, and geometric design).

### BEHAVIOURAL CHARACTERISTICS

Of the 10 items considered there was an excess of adverse features among the index group (table 4). There was a strong correlation between the parents' and the teachers' ratings (Spearman's rank correlation: r=0·292; p=0·02), and both sets of observers recorded the index group as being significantly more overactive, easily frightened, and clumsy. In addition the teachers rated the index group as being more fidgety. Both testers (NM and BLR) subjectively agreed that many extremely low birthweight children were inattentive or distractable.

### NEUROLOGICAL FINDINGS

Minor neurological signs were more common and more pronounced among the extremely low birthweight group compared with control subjects (table 5). This was especially true for dystonic movements, dysdiadochokinesia, and associated movements, all of which were found significantly more often among the extremely low birthweight children (table 6). The presence of these neurological signs correlated with the impairment score (all signs: $r^2$=0·235, p=<0·0001; pronounced signs: $r^2$=0·242, p=<0·0001).

Using the two tests described by Fog and Fog[10] the extremely low birthweight children had more mirror (p=0·011) and associated movements (p=0·009).

Table 4 *Behavioural data*

| | *Extremely low birthweight group* | | *Control group* | | $\chi^2$ | *p Value* |
|---|---|---|---|---|---|---|
| | *More* | *Less* | *More* | *Less* | | |
| **Parents' judgement:** | | | | | | |
| Irritable | 9 | 5 | 6 | 9 | | |
| Overactive | 25 | 2 | 10 | 4 | 9·54 | 0·009 |
| Difficult to handle | 10 | 12 | 8 | 16 | | |
| Easily frightened | 19 | 5 | 8 | 13 | 8·18 | 0·017 |
| Shy | 8 | 20 | 3 | 16 | | |
| Anxious | 16 | 3 | 18 | 1 | | |
| Headstrong | 23 | 3 | 18 | 1 | | |
| Temper tantrums | 4 | 9 | 10 | 10 | | |
| Clumsy | 12 | 5 | 4 | 15 | 9·05 | 0·011 |
| Fidgety | 21 | 6 | 13 | 12 | | |
| **Teachers' judgment:** | | | | | | |
| Irritable | 9 | 14 | 1 | 20 | | |
| Overactive | 13 | 16 | 3 | 8 | 13·5 | 0·001 |
| Difficult to handle | 10 | 13 | 3 | 20 | | |
| Easily frightened | 17 | 3 | 4 | 9 | 11·68 | 0·003 |
| Shy | 11 | 16 | 12 | 12 | | |
| Anxious | 24 | 4 | 15 | 6 | | |
| Headstrong | 12 | 11 | 7 | 12 | | |
| Temper tantrums | 5 | 16 | 1 | 20 | | |
| Clumsy | 20 | 4 | 4 | 9 | 22·79 | 0·0001 |
| Fidgety | 20 | 10 | 8 | 15 | 7·01 | 0·03 |

Because of the correlation between impairment score and both intelligence quotient (p=0·0001) and neurological signs (p=<0·0001), multiple regression analysis was carried out to explore the association between impairment score and birth weight (coded as a dichotomous variable: < 1251 g; > 1251 g), including demographic variables in the analysis (as indicated in table 2) and intelligence quotient. Using a forward stepwise technique, birthweight entered the model first ($r^2$: 0·21) and then intelligence quotient. These two variables contributed 25% of the variance in impairment score (F=20·92, p=<0·0001). No further demographic variables contributed significantly to the model. Of all outcome variables the total number of minor neurological signs present correlated best with impairment score ($r^2$: 0·24).

Table 5 *Minor neurological signs*

| | *No of minor neurological signs* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *0* | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* |
| Any abnormal signs: | | | | | | | | | | |
| Extremely low birthweight group | 0 | 3 | 6 | 7 | 5 | 11 | 8 | 6 | 1 | 6 |
| Control group | 6 | 5 | 5 | 6 | 13 | 9 | 6 | 2 | 1 | 0 |
| Pronounced abnormalities: | | | | | | | | | | |
| Extremely low birthweight group | 12 | 13 | 12 | 8 | 3 | 1 | 3 | 1 | | |
| Control group | 27 | 10 | 9 | 6 | 0 | 0 | 0 | 1 | | |

Extremely low birthweight group compared with control group: any sign p=0·03, pronounced signs p=0·002 (Mann-Whitney U test).

Table 6 *Neurological data*

| | *Extremely low birthweight group* | | | *Control group* | | | $\chi^2$ | *p Value* |
|---|---|---|---|---|---|---|---|---|
| | *None* | *Slight* | *Pronounced* | *None* | *Slight* | *Pronounced* | | |
| Fog test: | | | | | | | | |
| Mirror movements | 4 | 35 | 12 | 17 | 27 | 11 | 8·98 | 0·01 |
| Associated movements | 14 | 16 | 21 | 28 | 18 | 9 | 9·45 | 0·009 |
| Other signs: | | | | | | | | |
| Hypotonicity of limbs | 45 | 7 | 1 | 53 | 2 | 0 | | |
| Truncal unsteadiness | 38 | 15 | 0 | 46 | 9 | 0 | | |
| Dystonic movements | 23 | 25 | 5 | 37 | 17 | 1 | 7·42 | 0·02 |
| Dysdiadochokinesis | 5 | 19 | 29 | 14 | 24 | 17 | 7·94 | 0·02 |
| Finger/nose test | 46 | 5 | 2 | 54 | 1 | 0 | | |
| Finger placing | 36 | 16 | 1 | 41 | 10 | 4 | | |
| Finger opposition | 25 | 14 | 14 | 22 | 25 | 8 | | |
| Follow a finger | 25 | 15 | 13 | 35 | 15 | 5 | | |
| Circle-opposites | 42 | 8 | 3 | 49 | 5 | 1 | | |
| Circle-together | 20 | 17 | 16 | 30 | 16 | 9 | | |
| Heel walking: associated movements | 19 | 15 | 19 | 31 | 18 | 6 | 9·88 | 0·007 |

### PERINATAL CORRELATES

Twenty children (38%) had neonatal periventricular haemorrhages, 10 subependymal, eight intraventricular, and two parenchymal haemorrhages. Seven children (13%) had persistent parenchymal changes. No association between periventricular haemorrhage or parenchymal lesions and impairment score was observed (table 7).

Table 7 *Impairment score and neonatal ultrasound findings*

| *Ultrasound finding* | *No of infants* | *Impairment score* |
|---|---|---|
| No haemorrhage | 33 | 7·0 (0–12·5) |
| Subependymal | 10 | 5·5 (0–15·5) |
| Intraventricular | 8 | 6·0 (4–11) |
| Parenchymal (unilateral) | 2 | 1·5 and 4·5 |
| Persisting ventricular dilatation | 3 | 4·0, 10·0, and 10·5 |
| Small cysts (< 1 cm): | | |
| Right occipital cysts | 2 | 6·5 and 8·5 |
| Bilateral parietal cysts | 1 | 1·5 |
| Large cysts (> 1 cm): | | |
| Right occipital cyst | 1 | 4·0 |

Table 8 *Perinatal clinical factors. Values are shown as median (range) or number with factor, as appropriate*

| | |
|---|---|
| Birth weight (g) | 1050 (630–1250) |
| Gestation (weeks) | 28·5 (24–35) |
| Birth weight/gestational age standard deviation score* | −0·54 (−3·85 to +2.18) |
| Twin pregnancy | 12 |
| Antenatal problems: | |
| Bleeding <20 weeks | 6 |
| Antepartum haemorrhage as an indication for delivery | 8 |
| Pre-eclampsia as an indication for delivery | 8 |
| Prolonged membrane rupture > 24 hours | 9 |
| Mother taking β-agonists antepartum for longer than 12 hours | 20 |
| Mother taking steriods antepartum for longer than 24 hours | 13 |
| Fetal distress as an indication for delivery | 13 |
| Route of delivery: | |
| Breech | 12 |
| Caesarean section | 20 |
| Apgar score: | |
| At 1 minute | 4 (2–7) |
| At 5 minute | 9 (7–10) |
| Intubated at delivery | 30 |
| Ventilated before admission | 24 |
| Bruising noted | 14 |
| Hyaline membrane disease | 37 |
| Septicaemia | 7 |
| Abnormal movements | 4 |
| Fits | 8 |
| Ventilation (n=40) | 3 days (1–28) |

*Standard deviation score=birth weight-mean birth weight for gestation/standard deviation of birth weight.

Within this very low birthweight group no effect of birthweight, gestational age, or intrauterine growth could be shown. Analysis of single factors (table 8) showed that only an Apgar score at five minutes of less than seven was significantly associated with an impairment score at the age of 6 years (Mann-Whitney U test: p=0·014).

Forward stepwise multiple regression analysis showed that three perinatal variables were associated with impairment score. A decreasing Apgar score at five minutes, proven neonatal septicaemia, and the presence of abnormal movements were associated with higher (worse) scores (r: 0·566). Together these factors explained 32% of the variance in impairment scores.

## Discussion

Although major motor impairment or cerebral palsy is a common finding among extremely low birthweight infants who survive, few studies have considered the less severe impairments. The present study supports the hypothesis that such children have a range of motor problems from the most severe (those with cerebral palsy who were not included in this study) to less disabling impairments. Most of our study group (all of whom were considered neurologically normal) have obvious motor problems over the whole range of skills tested, including significant differences between index and control children in seven of the eight test items.

Using tests related to the currently used test of motor impairment, three previous studies have reported impaired motor performance in perinatally disadvantaged children born between 1960 and 1972; those weighing under 1000 g at birth,[4] under 1500 g,[13] and those born preterm.[14] Only the latter two studies included controls, and both showed impaired performance among their respective study groups over a wide range of tests encompassing intelligence quotient, perception, and behaviour. Our data confirm that such impairments are still common among children with the lowest birth weights despite improvements in care and survival. The association between intelligence quotient and motor impairment score (although it showed a weak correlation) was not linear, there being a wide scatter of results. The extremely low birthweight group did significantly less well on five of the subscales, two verbal items (information and arithmetic), and three performance items (picture completion, mazes, and geometric design). An association between clumsiness at school entry and later school problems, including poor arithmetic skills, has previously been noted.[15] Similarly, perceptual problems were reported in earlier studies of low birthweight[16 17] and very low birthweight[18] children, supporting our finding of poor scores on the three performance items. The discrepancy between verbal and performance scores did not vary significantly between our two groups. This is surprising in view of the commonly held belief that such a discrepancy denotes poor motor/perceptual skills. Other studies, however, have also failed to find this measure useful.[16 19] Language difficulties have been noted among very low birthweight children,[20] and may also contribute to the reduction in intelligence quotients.

The importance of having a control group must be stressed. In the general population an upward drift in intelligence quotients with time has been observed.[21] The scores of the index children observed in this study compare favourably with a notional mean of 100, but the use of classmate controls who, by their teachers' assessment, are performing at the same level as the study group, shows that this comparison is false. A recent very low birthweight cohort was found to have similar results to those reported here.[22] In addition, the median motor impairment score for controls (3·0) was higher than standardisation median of just under 1·0.[8] As with any test, the test of motor impairment may be interpreted in various ways. Although some children had a clear motor disability with high impairment scores, most seemed clinically normal. Controls are also essential for the interpretation of both minor neurological signs, which are subjective observations, and the assessment of behaviour profiles.

The control group were randomly selected by the head teachers, who were asked to select the child with the nearest birthday to the index case. Using such classroom controls a good socioenvironmental match was obtained, although the controls had a slight excess of social class I–III, and home owners. In contrast, the extremely low birthweight group had significantly fewer siblings and were more likely to be only children. These factors would operate in favour of the extremely low birthweight group.[23] The measures on which this match are assessed are necessarily crude. A recent study reported that most of the variance in outcome at 10 years between low birthweight children (< 2500 g) and well matched controls could be explained in socioenvironmental terms.[17] In so far as we have been able to control for such factors (table 2) no significant influence has been shown. We believe that the differences in motor impairment score shown here are of such a magnitude that they rule out such a influence. Indeed, despite the anticipated weak correlation between intelligence quotient and motor impairment score, the most important correlate of the six year impairment score was the birthweight group.

The inclusion of a detailed neurological examination shows that minor neurological signs are often found among normal 6 year olds, but are especially common among extremely low birthweight survivors, who had significantly more dyskinesia, dysdiadochokinesia, and dystonia. Low birthweight children with an excess of 'soft' neurological signs have been reported to receive more special education and more psychiatric referrals.[16 24] In addition, although motor difficulties may disappear at a later age, children with 'soft' signs identified at early school age continue to show minor neurological deviancy at 10[16] and 17 years of age,[25] together with affective and anxiety disorders. These 'soft' signs comprise a mixture of items ranging from minor neurological signs as defined here to items from motor performance tests. All the six year outcome variables described in the present study are statistically related, but using multiple regression analysis the number of minor neurological signs has the strongest correlation with motor impairment score, suggesting an organic basis for the observed motor impairment. Recent studies have reported a high frequency of attention/deficit disorder among low birthweight[16] and very low birthweight[22] children. This diagnostic category[26] comprises several different characteristics, including neuromotor, behavioural, and attentional problems, many of which were present in our children. In this study there was good agreement between both parents and teachers that the index children were more likely to be clumsy, overactive, and more easily frightened. Teachers considered the index children to be more fidgety. During the examination both examiners independently recorded that many of the extremely low birthweight children subjectively had short attention spans and were more distractable. The test of motor impairment comprises short items that are easy to understand and perform. It is unlikely that attentional deficits contributed greatly to the pronounced differences in motor skills that were seen, though clearly they would contribute to school performance.

Previous studies of very low birthweight children have had only limited success in the definition of perinatal antecedents of *major* disabilities. Individual studies have identified comparatively few clinical associations, such as low Apgar scores,[27] mechanical ventilation,[28–30] and neonatal convulsions.[27 28 31] In a further study no consistency was found in factors predictive of cerebral palsy or developmental retardation between two adjacent hospitals.[32] This lack of consistency is perhaps not surprising in view of current ideas that localised periventricular brain injury, rather than a specific series of clinical events, is important in the generation of later disabilities. None the less, these studies indicate some of the predisposing factors in the generation of such brain injury. The association of adverse clinical perinatal factors with later motor impairments in this study suggests that such impairments may indeed be acquired in the perinatal period, and that further studies are indicated.

It is of interest that the three clinical factors identified by this study are similar to the associates of periventricular leucomalacia found by Sinha *et al.*[33] Cystic periventricular leucomalacia is clearly associated with later major impairments, and changes on cerebral ultrasound scanning correlate well with later cerebral palsy.[6] Less severe ultrasound changes may be associated with lesser impairments, but the evidence presented in this study does not support this hypothesis. Ultrasound scans were, however, performed with the technology available in 1980–81. Higher frequency scan heads and better awareness of the natural history of minor ultrasound findings[34] may reveal a more subtle association not identified by this study. It is, therefore, as yet not clear whether children with no cerebral palsy but poor motor skills have suffered similar but less severe brain injuries than those children with cerebral palsy.

Although considered to be performing satisfactorily in the infant school, this group of extremely low birthweight children have a wide range of minor abnormalities of motor, neurological, cognitive, and behavioural function. These problems are likely to become quantitatively more important when greater demands are made at junior school age and beyond. Children born before recent improvements in neonatal care have frequent educational problems.[16 17 20 35] Despite recent improvements in perinatal care it seems likely that such problems persist. Future research should be directed at defining the aetiology of such impairments and at their amelioration or prevention.

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# Cerebral palsy in two national cohort studies

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SUMMARY The prevalence of cerebral palsy in the 1958 British Perinatal Mortality Survey and the 1970 British Births Survey remained constant at 2·5/1000 births (40 and 41 cases, respectively). The prevalence at 10 years was higher in the 1970 cohort in which all children with cerebral palsy survived, whereas 22% of the cases in the 1958 cohort died during the first 10 years of life.

A case-control study matched three controls for social class, maternal age, parity and marital state, and a further three controls for the infant's sex, gestation, and birth weight. Comparison of cases and controls showed no consistent differences in social and environmental factors, history of pregnancy, labour, or delivery. Important differences were found in the incidence of respiratory and neurological symptoms in the neonatal period.

These prospective data derived from two whole populations of births support the hypothesis that most cases of cerebral palsy are not associated with adverse obstetric factors, and confirm that neonatal neurological symptoms are associated with subsequent cerebral palsy.

The association between perinatal mortality and childhood impairment, especially cerebral palsy, remains uncertain. It has often been assumed that factors relating to mortality, especially those caused by asphyxia and cerebral trauma at birth, would also be associated with a high risk of impairment among survivors. This hypothesis has recently been challenged by Ounsted who pointed out that the data on which the original concept of a 'continuum of reproductive casualty' was based were open to criticism.[1]

We have examined the prevalence of, and risk factors for, cerebral palsy in two national cohort studies: both were similar in their design and methods but took place 12 years apart. During those 12 years there were reductions both in the rate of stillbirths (from 22 to 13/1000 total births), and in neonatal mortality (from 16 to 12/1000 live births).

Whether or not causally associated with this drop in mortality, obstetric practice had changed and become more interventional. The proportion of births delivered in consultant units increased from 48% to 66%, caesarean section deliveries increased from 3% to 5%, inductions of labour increased from 13% to 26%, and forceps or ventouse deliveries increased from 5% to 9%. In 1958, 8% of women had labours lasting longer than 24 hours for the first stage, and 21% in excess of one hour for the second stage.[2] By 1970 these proportions had dropped to 4% and 12%, respectively, and the mortality associated with cerebral trauma at birth fell from 3/1000 in 1958 to 0·4/1000 total births in 1970.[3]

## Subjects and methods

### THE BIRTH SURVEYS

The 1958 British Perinatal Mortality Survey aimed to study all births in England, Scotland, and Wales during the week 3–9 March. Detailed questionnaires were completed by the midwives soon after delivery using clinical notes and information obtained by interviewing the mothers. It is estimated that 98·5% of total births were included in the survey.[4 5] The 1970 British Births Study used a similar method, and included all births in the week 5–11 April in the United Kingdom.[3 6] Only 2% of births were thought to have been omitted.

### FOLLOW UP

The children born in 1958 were subsequently traced and followed up at the ages of 7, 11, and 16. At each visit the parent was interviewed about the medical history of the child (including admissions to hospital and visits to outpatient departments) and asked whether the child had any impairment, disability, or handicap. At each of these follow up visits the clinical medical officer examined the child and noted any problems. The teacher was also asked to note any problems and to assess the child's ability.

For the 1970 birth cohort, children residing in England, Scotland, and Wales were followed up at the ages of 5 and 10. At the age of 5 a complete medical history was obtained from the mother, and the health visitor concerned with the child. At the age of 10 a complete medical history was again taken from the mother, and the clinical medical officer examined the child. Similar questions were asked to those in the 1958 survey, and once again the child's teacher was asked to participate.

For all children from both surveys who had what could have been cerebral palsy the hospital records were obtained, with the local consultant's permission. In addition, death certificates of all children who had died in the period between birth and the follow up were reviewed. Those with a record of cerebral palsy were investigated in more detail where possible. Cases with unequivocal evidence of postnatal causation were omitted. One case, who seemed to have cerebral palsy in the first year of life but was later normal, was not included.

### DEFINITIONS

*Cerebral palsy.* A non-progressive disorder of movement or posture resulting from damage to the developing brain. 'Acquired' cases (resulting from an insult after the neonatal period) were not included.

*Prevalence.* This was the number of cases of cerebral palsy surviving the neonatal period/1000 neonatal survivors (excluding acquired cases).

*Birth weight.* The baby was weighed within a few hours of birth. The birth weights in both surveys were measured in ounces and converted to grams for analysis.

*Gestation.* This was calculated as the number of completed weeks elapsing from the date of the first day of the last menstrual period to the date of delivery. Women with uncertain dates were analysed separately.

*Stillbirth.* This was defined as the birth of a dead fetus of 28 weeks' gestation or more (or a weight of 1000 g or more in the absence of an accurate estimate of gestational age).

*Parity.* The number of previous pregnancies resulting in a live or stillbirth.

*Social class.* This was coded using the classifications of the husband's occupation developed by the Registrar General for England and Wales.[7 8] For both surveys, all single, widowed, separated, or divorced women who did not have a partner with an occupation coded on the questionnaire were analysed separately—the unsupported mothers.

### CASE-CONTROL STUDY

As birth weight and gestation are known to be associated with cerebral palsy, it was felt important to match on these factors to identify other features of cerebral palsy. In order to assess whether possible associations with social class, maternal age, and parity accounted for the birth weight and gestation effects, a second set of controls was chosen. There were thus two sets of three controls for each case, so that each case had six matched controls.

Control series A comprised three infants matched for age of the mother at the birth of her child, parity, social class, marital status at the time of delivery, and whether the child was a single or multiple birth.

Control series B comprised three infants matched for birth weight, gestation, certainty of the date of the last menstrual period, sex of the child, and whether the child was a single or multiple birth.

## Results

### OVERALL PREVALENCE

Of the children born in the week 3–9 March 1958, 16 751 survived the neonatal period. Of these 40 developed cerebral palsy, giving a prevalence of 2·4/1000. Of the children born in Great Britain in the week 5–11 April 1970, 16 136 survived the neonatal period, and 41 had cerebral palsy (prevalence 2·5/1000). These figures are in remarkable agreement with those of the Isle of Wight (2·6/1000),[9] Watford (2·5/1000),[10] and the United States Collaborative Perinatal Project (which reported a prevalence of 2·5/1000 after excluding the mildly affected and the acquired disorders).[11]

### SURVIVAL

All children with cerebral palsy born in 1970 survived until the age of 10, whereas nine of the 40 cases born in 1958 (23%) had died by 10 years. Seven deaths occurred before 7 years and were identified from death certificate records. Of the 33 children who were seen at the age of 7 and described as having cerebral palsy, two subsequently died (one in a road traffic accident) before the 10 year assessment.

Consequently, although the prevalence of cerebral palsy in the neonatal period remained static between the two cohorts, there was a pronounced increase in prevalence at the age of 10 from 1·9/1000 in 1958 to 2·6/1000 in 1980.

### BIRTHWEIGHT SPECIFIC PREVALENCE

Only 17 infants weighing under 1500 g at birth from the 1958 cohort survived the neonatal period, compared with 53 from the 1970 cohort. In the study involving the children born in 1958, however, only two children found to have cerebral palsy weighed less than 1500 g at birth, and in the 1970 cohort there was only one (table 1). In 1970 there was an increase in the risk of cerebral palsy among the low birthweight babies, but a slight decrease among those who weighed 3500 g or more at birth.

Table 1 *Prevalence of cerebral palsy by birth weight*

| *Birth weight (g)* | *Prevalence of cerebral palsy/1000 survivors at 28 days* | |
|---|---|---|
| | *1958* | *1970* |
| <1500 | 117·6 (2) | 18·9 (1) |
| 1500–1999 | 10·5 (1) | 21·1 (4) |
| 2000–2499 | 6·0 (4) | 12·5 (10) |
| 2500–2999 | 4·1 (12) | 2·3 (7) |
| 3000–3499 | 1·3 (8) | 1·4 (9) |
| ≥3500 | 2·1 (13) | 1·4 (8) |
| Total <2500 | 9·0 (7) | 14·4 (15) |
| Total ≥2500 | 2·2 (33) | 1·6 (24) |
| Total including those of unknown birth weight | 2·4 (40) | 2·5 (41) |

Actual numbers are shown in parentheses.

### CASE-CONTROL STUDY

#### *Social factors*

As those in control series A were matched on social class and marital state there were no striking socioeconomic or environmental differences between them and the index cases. Using control series B, there was no evidence of differences by region, household overcrowding, ethnic group, or educational background.

#### *Maternal health*

The mother's age, parity, prepregnancy weight and height, smoking habit, and attendance for antenatal care were not associated with the subsequent development of cerebral palsy in the baby. There was no evidence that mothers of index cases had more complicated pregnancies: in particular there was no increase in the incidence of pre-eclampsia, bleeding, or anaemia during their pregnancies.

#### *History of labour*

The mothers of index cases were slightly (but not significantly) more likely to have labour induced. Among the children born in 1958, there were significantly more index children born after the membranes had been ruptured for at least 24 hours when compared with the control series A, but the association was not apparent among the 1970 cases. Neither the first nor second stages of labour differed in duration, nor was there a significant difference in the place of delivery or the type of analgesia given to the mother. There were only four cases of cerebral

Table 2 *Signs of asphyxia, 1970 only. Results are expressed as No (%)*

| | *Index cases (n=41)* | *Control series A (n=121)* | *Control series B (n=121)* |
|---|---|---|---|
| Time taken to establish regular respirations: | | | |
| <1 minute | 18 (44) | 91 (75) | 87 (72) |
| 1–3 minutes | 14 (34) | 27 (22) | 25 (20) |
| >3 minutes | 9 (22) | 3 (3) | 9 (7) |
| | | p<0·0001* | p<0·01* |
| Resuscitation method: | | | |
| None | 5 (12) | 33 (27) | 23 (19) |
| Positive pressure ventilation | 2 (5) | 0 | 1 (1) |
| Endotracheal tube | 4 (10) | 2 (2) | 3 (3) |
| Other oxygen | 20 (49) | 28 (23) | 31 (26) |
| Other physical | 10 (24) | 60 (49) | 63 (52) |
| | | p<0·0001* | p<0·0001* |
| Administration of oxygen: | | | |
| None | 15 (37) | 91 (75) | 85 (71) |
| By face mask | 7 (17) | 10 (8) | 11 (9) |
| By face funnel | 10 (24) | 13 (11) | 17 (14) |
| Other | 9 (22) | 7 (6) | 7 (6) |
| | | p<0·0001* | p<0·001* |

*p Values compared with index cases.
Numbers vary in each category according to number of controls on whom data was available.

palsy who had breech deliveries, compared with 13 birth weight/gestation matched controls. In contrast, six index cases were delivered by caesarean section compared with 11 birth weight/gestation controls. Thus there was no evidence that operative delivery affected outcome.

### *The baby*

Although there was a preponderance of boys (26/40) among the cases of cerebral palsy in the 1958 cohort, this difference was not significant and was not confirmed in the children in the 1970 cohort (23/41 boys). Compared with control series A, children with cerebral palsy were significantly more likely to be of low gestation or low birth weight, or both, than controls.

There was a strong association with time to onset of regular respirations, an excess of index cases taking longer than one minute to establish breathing (table 2). Children with cerebral palsy were more likely to have been given oxygen after birth than control cases. Index cases were more often admitted to a special care baby unit, and nursed in an incubator (table 3).

Among specific problems occurring in the first week, highly significant associations existed with 'breathing difficulties', cyanotic attacks, and cerebral irritation. These associations remained significant even when the controls of the same sex, birth weight, and gestation were compared (table 4).

## Discussion

There are both advantages and disadvantages in using the two present data sets to identify the possible causes of cerebral palsy. The principle advantages are that they cover a whole population of births, and the data were objective and gathered prospectively. They suffer from none of the biases of retrospective recall, and ascertainment is thought to have been almost complete. The defect lies in the lack of fine detail that might affect interpretation of the results.

We have shown in this study that, although there had been pronounced changes in obstetric practice and perinatal mortality between two periods of time—for example the incidence of cerebral trauma at birth had reduced considerably—the prevalence of cerebral palsy remained static.

Though the overall prevalence of cerebral palsy is unchanged, there is evidence in this and other studies that the birthweight specific risks of cerebral palsy have changed with the increased survival of more low birthweight infants.[12 13] It is possible that the increased contribution of low birthweight babies to the population of infants with cerebral palsy has been matched by a decrease in the contribution from babies weighing more than 3500 g.

Overall, the proportion of children with cerebral palsy who had low birth weights was lower in these two British cohorts than that reported in the hospital

Table 3 *Nursing dependency, 1970 only*

| | *Index cases* | *Control series A* | *Control series B* |
|---|---|---|---|
| No (%) admitted to special care unit at any time during first week | 17/41 (42) | 10/121 (8)* | 25/122 (20)* |
| No (%) nursed in incubator on first day | 15/41 (37) | 10/117 (9)* | 24/121 (20)* |

*p<0·001 compared with index cases.

Table 4 *Signs and symptoms in first week of life, 1970 only. Results are expressed as No (%)*

| | *Index cases* | *Control series A* | *Control series B* |
|---|---|---|---|
| Breathing difficulties | 13/40 (32) | 3/121 (3)*** | 6/122 (5)*** |
| Cyanotic attacks | 9/41 (22) | 0/121*** | 6/119 (5)** |
| Fits or convulsions | 2/39 (5) | 0/122 | 0/120 |
| Cerebral irritation | 10/40 (25) | 3/122 (3)*** | 3/118 (3)*** |
| Jaundice | 12/40 (30) | 18/121 (15) | 37/121 (31) |
| Congenital defect | 4/41 (10) | 3/122 (3)* | 5/123 (4) |
| Cephalohaematoma | 0/41 | 1/122 (1) | 1/122 (1) |
| Sticky eyes | 0/40 | 9/120 (8) | 10/119 (8) |
| Umbilical discharge | 2/40 (5) | 1/120 (1) | 2/120 (2) |
| Other illness | 4/40 (10) | 9/123 (7) | 0/119 |

*p<0·05; **p<0·01; ***p<0·001.

based United States National Collaborative Perinatal Project,[14] in which 22% of the cases of cerebral palsy were born weighing less than 2000 g. These national cohort studies, however, were undertaken before the widespread introduction of intensive care in the 1970s. Evidence now suggests that there has been an increase in cerebral palsy among survivors with low birth weights since 1970, but this increased survival has not made a significant contribution to the overall rate of cerebral palsy. Rates of cerebral palsy are thus not a good index of the impact or quality of neonatal intensive care.[15]

This study lends no support to the contention that infants with cerebral palsy were born after abnormal pregnancies, labours, or types of delivery. Once delivered, however, they were more likely to have an abnormal neonatal course. In both cohorts, asphyxia (measured as time to onset of regular respiration) seemed to be a strong predictor of cerebral palsy. The lack of association with intrapartum factors recognised to lead to asphyxia (for example, a prolonged second stage), however, suggests that the delay in onset of respiration reflects a baby compromised by events or developmental aberrations in early fetal life.

Similar conclusions on the causes of cerebral palsy have been reached from other population studies, using multivariate analyses of risk.[16] Data from both Australia[17] and the United States[16] have led to similar estimates (3–13%) of the proportion of cerebral palsy that might have been caused by intrapartum damage.

There is no evidence from these cohort studies to indicate that changes in obstetric practice would alter the prevalence of cerebral palsy. Few children with cerebral palsy are damaged during birth[17]; improvements in obstetric and neonatal care can be expected to reduce the perinatal mortality rate, but not the prevalence of cerebral palsy in the population.[12 18] In particular there is no evidence that increases in the numbers of caesarean sections will reduce the number of cases of cerebral palsy.

In conclusion, most cases of cerebral palsy are not associated with perinatal factors, though neurological symptoms in the neonatal period are strongly associated with subsequent cerebral palsy. This study offers no evidence to support the concept of a 'continuum of reproductive casualty'; indeed, it lends support to Freud's assertion in 1897 that 'difficult birth in itself is merely a symptom of deeper effects that influence the fetus'.[19] We hope that research over the next 90 years will throw more light on the nature of these deeper effects.

We thank all who took part in these national cohort studies: the midwives, health visitors, medical officers, administrators, teachers, and especially the parents. For this particular study we also thank the records officers and consultants for giving us permission to view the children's clinical records, Richard Belli for carrying out the computing, and Yasmin Iles for typing the manuscript.

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# Cellobiose:mannitol differential permeability in small bowel disease

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SUMMARY Cellobiose and mannitol absorption were studied in patients with suspected abnormal function of the small bowel mucosa. The urinary cellobiose:mannitol ratio was increased in subtotal villous atrophy, iron deficiency anaemia, and small intestinal Crohn's disease. The test seems a sensitive indicator of the integrity of small bowel mucosa.

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A number of non-invasive dual sugar permeability tests have been proposed, based on the theory that villous atrophy reduces absorption of monosaccharides, and mucosal damage increases permeability of disaccharides, particularly if the test solution is hyperosmolar.[1] The disaccharide cellobiose and the sugar alcohol mannitol, given orally in hyperosmolar solution, provide a sensitive test of mucosal function of the small bowel in adults.[2] The ratio between percentage recoveries of the two probe molecules in a timed urine collection—the cellobiose:mannitol ratio—is raised if the mucosa is damaged. Factors common to the urinary excretion of both molecules such as failure of ingestion of the fixed dose, adequacy of timed urine collections, rapidity of intestinal transit and renal clearance, are eliminated. We have therefore evaluated the test in children with suspected disease of the small intestine.

## Patients and methods

A jejunal biopsy and the cellobiose mannitol test were carried out at the same time on 49 occasions in 48 children (mean age 4·8 years, range 6 month—16 years) with symptoms suggestive of malabsorption. After fasting overnight and emptying the bladder a 1500 milliosmolar solution (cellobiose 33 g/l, mannitol 13 g/l, lactose 133 g/l, and sucrose 133 g/l) was given in a dose of 150 ml/1·73 $m^2$. An hour later a jejunal biopsy was taken under fluoroscopic control. After the biopsy the patients were encouraged to drink water to promote a diuresis. Urine was collected for five hours. Cellobiose was measured enzymatically and mannitol colorimetrically as previously described by Strobel *et al*[2] and the ratio of their percentage recoveries calculated. The biopsy specimen was processed for conventional histological examination and reported without knowledge of the cellobiose:mannitol ratio.

The cellobiose mannitol test was also carried out in 13 healthy children (mean age 6·8 years, range 1·6–11·66) who were either of normal stature (n=9) or of short stature with normal growth velocity (>25th centile height velocity) and no intestinal symptoms (n=4), seven healthy adults, and three children with moderate Crohn's disease of the small bowel (score 50–60 Lloyd-Still classification[3]).

Non-parametric statistical analysis was by the Mann-Whitney U test.

## Results

The test solution was well tolerated; no children had diarrhoea despite the lactose load and no difficulties accompanied the performance of the two tests together.

There was no significant difference between the cellobiose:mannitol ratio in normal adults and children (figure, table). Eight biopsy specimens showed subtotal villous atrophy; the cellobiose: mannitol ratios in these cases were significantly greater than in both normal controls ($p<0{\cdot}01$) and children with normal biopsy specimens ($p<0{\cdot}01$). A cellobiose:mannitol ratio of 0·035 corresponded to two standard deviations above the mean for our

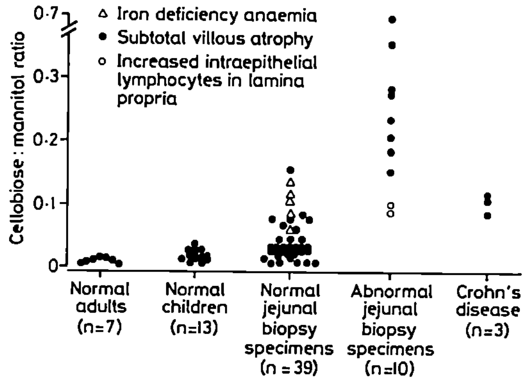

Figure *Cellobiose:mannitol ratios for normal subjects and patients.*

Table *Median (interquartile range) cellobiose:mannitol ratios and percentage recovery of cellobiose and mannitol in normal subjects and patients*

| | *Normal adults (n=7)* | *Normal children (n=13)* | *Subtotal villous atrophy (n=8)* | *Normal jejunal biopsy specimen, not iron deficient (n=34)* | *Normal jejunal biopsy specimen, iron deficient (n=5)* |
|---|---|---|---|---|---|
| Cellobiose:mannitol ratio | 0·009 (0·0092) | 0·016 (0·015) | 0·24 (0·147) | 0·027 (0·039) | 0·105 (0·054) |
| Cellobiose recovery (%) | 0·29 (0·22) | 0·34 (0·24) | 1·56 (1·04) | 0·14 (0·41) | 1·53 (0·93) |
| Mannitol recovery (%) | 33·7 (10·0) | 23·6 (13·7) | 4·66 (4·69) | 9·4 (13·4) | 13·13 (8·35) |

normal children. Fifteen of 39 children with normal biopsy specimens had cellobiose:mannitol ratios of greater than 0·035. Five had iron deficiency anaemia (haemoglobin concentration <100 g/l, mean corpuscular volume <70, and serum ferritin concentration <12 μg/l), two had food allergies, two had diarrhoea, one had recently had gastroenteritis, one had a family history of coeliac disease and positive antibodies to reticulin, and four were considered normal. Two children with coeliac disease on gluten free diets whose cellobiose:mannitol ratios were 0·039 and 0·095, respectively, had increased lymphocytes in the lamina propria but normal villi and crypts.

Individual sugar recoveries showed significantly decreased mannitol ($p<0·01$) and increased cellobiose ($p<0·01$) in those with subtotal villous atrophy when compared with normal controls. Similar cellobiose recovery was seen in iron deficiency anaemia and subtotal villous atrophy (table).

## Discussion

The cellobiose:mannitol ratio in normal children and adult controls corresponds well with previously published adult values.[2]

Hyperosmolar solutions have a potential risk of inducing osmotic diarrhoea, but this did not occur in the subjects studied.

If the test was used as a screen for subtotal villous atrophy and a value of 0·035 (two standard deviations above the mean for normals) was taken, above which a jejunal biopsy was undertaken, the sensitivity would be 100%, the specificity 62%, and the predictive value 35%. Taking a value of 0·1 would not reduce the sensitivity but would increase the specificity to 87% and the predictive value to 62%.

A study in adults using this hyperosmolar test solution has shown functional abnormality despite normal crypt and villous architecture,[2] particularly if the intraepithelial lymphocyte count is high. By contrast, using lactulose and mannitol in an isotonic solution in children, abnormalities of permeability in the presence of increased intraepithelial lymphocytes were not found.[4] Thus increasing tonicity of the test solution seems to increase sensitivity and reduce specificity. The two children in our study with increased intraepithelial lymphocytes both had high cellobiose:mannitol ratios, as did some of our patients with normal jejunal morphology, all of whom had biopsies taken because of suspected malabsorption. This might represent a functional abnormality of small intestinal mucosa, particularly in the five patients with iron deficiency anaemia who had appreciably increased cellobiose absorption. Reversible mucosal damage with associated steatorrhoea has been previously described in children with severe iron deficiency[5]; mucosal damage not apparent on light microscopy may have been present in these patients.

We have shown by giving a hyperosmolar solution that there is increased absorption of disaccharides in children with subtotal villous atrophy. This has previously been shown in adults[2] but not in children.[6]

The cellobiose:mannitol permeability test is a sensitive and well tolerated non-invasive screening test of small bowel function. Values of more than 0·1 suggest that a jejunal biopsy specimen should be taken. The test may be used to monitor a gluten challenge, and possibly also the response to treatment in small bowel Crohn's disease. Difficulties in interpretation may occur in patients with iron deficiency anaemia.

We thank Dr IC Talbot for histological reports on the jejunal biopsy specimens.

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# Focal glomerulosclerosis treated with heparin

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SUMMARY A boy with focal glomerulosclerosis as a result of nephrotic syndrome became unresponsive to corticosteroids and cyclophosphamide. He was given prolonged subcutaneous heparin with reduction in proteinuria, return of corticosteroid sensitivity, and no further deterioration (possibly improvement) in histological appearance. He remained completely well after five years.

Focal glomerulosclerosis usually progresses to death of the kidneys. It commonly presents with nephrotic syndrome, and initial histological examination may miss the focal lesions, and lead to a mistaken diagnosis of nephropathy with minimal lesions.[1] We report a 9 year old boy who presented in this way, and became unresponsive to corticosteroids and cyclophosphamide. His subsequent cure seemed to be the result of treatment with heparin.

## Case report

A boy aged 9·5 years presented with severe oedema, hypoproteinaemia (total serum protein concentration 44 g/l), and a 24 hour urinary protein excretion of 1·36 g. His course is illustrated in the figure. Treatment with corticosteroids resulted in clinical remission and the disappearance of the proteinuria. Three months later he relapsed, but again responded to treatment with steroids.

After a further three months he relapsed and was referred to one of us (DRL). Prednisolone 40 mg/day was given and examination of a renal biopsy specimen under electron microscopy showed 15 glomeruli with no evidence of focal glomerulosclerosis, but evidence of fusion of the podocytes consistent with minimal change nephropathy. His urine became free of protein after six days, when cyclophosphamide 2·5 mg/kg/day was added to his treatment regimen for eight weeks. After four weeks he relapsed; he responded to steroids but six days before completing the course of cyclophosphamide he relapsed again. A course of prednisolone did not clear his proteinuria completely, and after eight weeks reduction in dosage was attempted, but increased oedema and proteinuria required higher doses. After his sixth relapse he was given a further course of cyclophosphamide (4·8 mg/kg/day) for eight weeks.

During the next four months he became unresponsive to prednisolone 2 mg/kg/day, his urinary protein excretion remained between 4 and 11 g/day requiring intravenous courses of protein and diuretics for anasarca. Examination of a second biopsy specimen showed 31 glomeruli with widespread mild mesangial expansion, sclerosis, and hypercellularity. Discrete, sclerosing, segmental lesions were present and there was almost complete podocyte fusion. The appearance was considered typical of focal glomerulosclerosis.

After a further intravenous course of protein for anasarca it was decided to give heparin, initially intravenously for three days, but there was no obvious response. Indomethacin 25 mg three times a day for a month did not reduce the urinary protein excretion, and further intravenous protein was given.

At the age of 10·8 years a further intravenous course of heparin was given for 3·5 days, but this did not help and nephrectomy for the control of proteinuria and anasarca was considered. The parents requested a longer trial of heparin, which was then given subcutaneously for three months with a target blood concentration of 0·2 U/ml. The range achieved was 0·11 to 0·64 on an average daily dose of 550 U/kg/day. Frequent 24 hour specimens of urine were examined to determine protein excretion and these are summarised in the figure. Proteinuria rapidly decreased, and remained low but after three months the effect seemed to lessen. From day 5 fluid retention was less than it had been

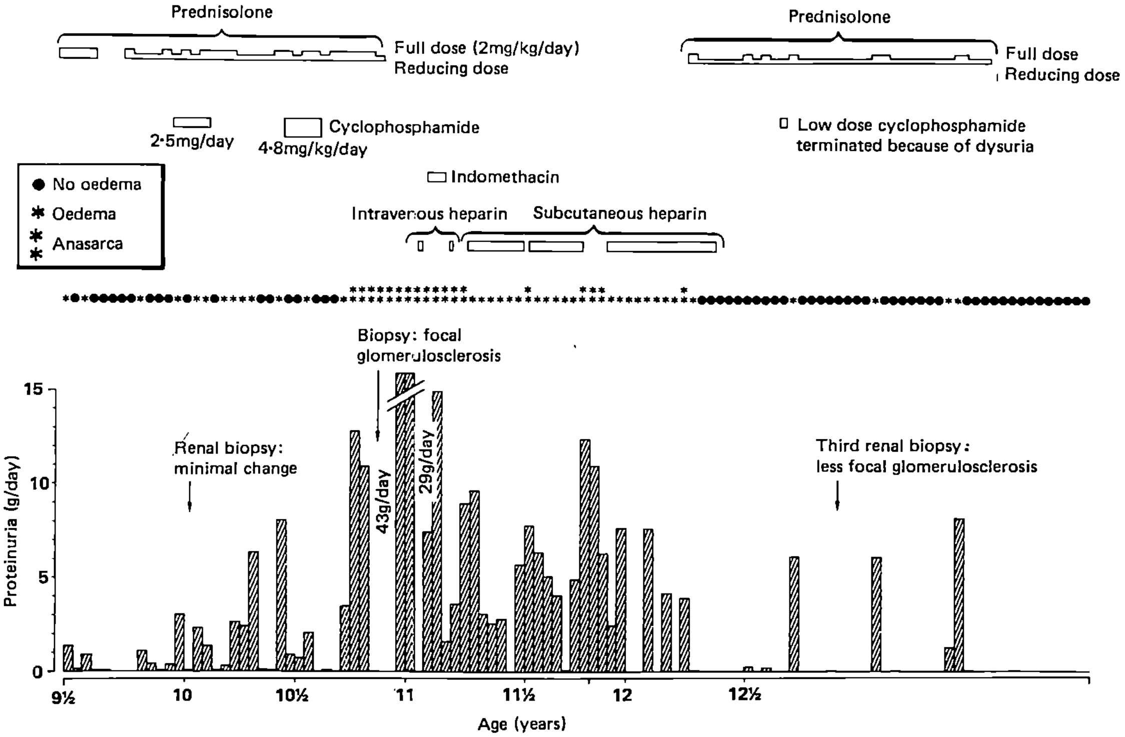

Figure *A patient with frequently relapsing nephrotic syndrome became unresponsive to corticosteroids. After treatment with subcutaneous heparin the concentration of protein in the urine gradually reduced, and the patient again responded to corticosteroids.*

in the previous six months. On stopping the heparin proteinuria and oedema increased. After one week, at the request of the patient and parents, subcutaneous heparin was restarted. Protein excretion over 24 hours steadily declined to 70 mg after six weeks, but rose again to about half what it had been before the heparin had been given.

When heparin was stopped after three months, troublesome oedema recurred and urinary protein excretion rose to 11 g/day. Yet another course of heparin led to diminished proteinuria (lowest value 2·4 g) and easier control of fluid retention. After six months, however, anasarca requiring intravenous protein administration again developed. He was given prednisolone (2 mg/kg/day). Ten days later he had a dramatic diuresis, and the proteinuria cleared. Heparin was stopped and two days later all diuretics were withdrawn for the first time in 16 months. Serum creatinine concentrations measured before his first course of heparin and after the last course were identical at 500 μmol/l.

Two further relapses of nephrotic syndrome in the next four months responded to short (five to seven day) courses of prednisolone. While in remission after the second episode, he was given cyclophosphamide but this was stopped after a week because of dysuria.

When he was 13 years old, 21 months after heparin was first given subcutaneously and two years after focal glomerulosclerosis was diagnosed, examination of a third biopsy specimen showed sporadic, totally obsolescent glomeruli, and mild diffuse (but variable) mesangial hypercellularity in the remainder. One of 27 glomeruli in the biopsy specimen had segmental solidification as a result of sclerosis and hyalinosis occupying about one third of the tuft. Electron microscopy showed widespread re-establishment of podocytes with only sporadic fusion.

More than five years have elapsed since the second renal biopsy specimen showed focal glomerulosclerosis. He remains well, has a full time job, and there is no evidence of proteinuria, renal failure, or hypertension.

## Discussion

The course of this boy's focal glomerulosclerosis is unusual and his return to complete health seems to be as a result of treatment with heparin. Cameron *et al*[2] in a 9·5 year follow up of 40 consecutive patients with focal glomerulosclerosis found only four with normal renal function and no urinary protein excretion. None of the 12 children that they studied had both normal renal function and normal urine. Their actuarial analysis showed a trend for children to fare worse than adults. Those who presented with nephrotic syndrome had a poorer outcome than those who were diagnosed after biopsy specimens had been taken for proteinuria.[2] Our patient was both a child and presented with nephrotic syndrome.

Tejani *et al* divided their parents with nephrotic syndrome and focal glomerulosclerosis into 'steroid sensitive' and 'steroid resistant' at the outset. Those who were initially resistant reached end stage renal failure a mean (SD) of 2·3 (1·3) years earlier than those who were initially sensitive (10·5 (5·8) years).[3] They could find no difference, however, in the rate of progression once focal glomerulosclerosis had been diagnosed from a biopsy specimen. Compared with their results the absence of renal failure and urinary abnormality in a patient five years after diagnosis is remarkable.

Srivastava *et al* observed that nephrotic children with late steroid resistance, focal glomerulosclerosis, and cyclophosphamide resistance constitute a group with poor prognosis.[4] In a search of the published reports, we found only one patient with nephrosis, focal glomerulosclerosis, and resistance to steroids and alkylating agents who survived with no renal failure and no proteinuria. He was 2·5 years old at presentation and focal glomerulosclerosis was not diagnosed until he was 9·5 years old. Regrettably follow up after the diagnostic biopsy specimen was only 1·5 years.[4]

Thus on clinical grounds our child did unusually well. Strikingly, in all the papers cited where a further biopsy was carried out after the diagnostic one, progression of the focal glomerulosclerosis was found. In our case, examination of the repeat biopsy specimens did not show any progress, and it is postulated that this was due to the treatment with heparin.

The rationale for giving heparin was given in the paper by Seiler *et al* in which they reported that they had reversed the protamine induced loss of glomerular podocytes in rats by infusion of heparin.[5] Though our patient did not have overt renal failure, nephrectomy was considered because of his gross proteinuria and debilitating anasarca. A prolonged course of subcutaneous heparin reduced his proteinuria and fluid retention sufficiently for him to return to school, where he played soccer (in goal), and cricket (as opening batsman—with a helmet in view of the heparin induced clotting deficiency—this activity was against DRL's instructions). When the heparin was stopped, the proteinuria increased and the anasarca returned. It was largely in response to parental urging that second and third courses were given with improvement on both occasions. After the third course he became sensitive to steroids again; later examination of a biopsy specimen showed no progression, and possible improvement.

All these responses are most unusual and we suggest that heparin played a part in their occurrence. At the very least it can be claimed that heparin reduced his proteinuria, allowed a return to normal life, and bought time during which he became sensitive to corticosteroids again. It may be that heparin had a more fundamental effect on his renal lesion.

Though more studies are needed, the poor prognosis of children with focal glomerulosclerosis and its well documented recurrence in transplanted kidneys[2 3] suggests that a trial of subcutaneous heparin may be justified in an attempt to improve the outcome of childhood nephrotic focal glomerulosclerosis.

We thank the staff of the divisions of paediatrics, pathology, and haematology of Flinders Medical Centre who contributed to the care of this patient.

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# Porencephaly and optic hypoplasia in neonatal isoimmune thrombocytopenia

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SUMMARY Five children with prenatal intracerebral damage associated with neonatal isoimmune thrombocytopenic purpura are described, and characteristic neurological features listed. These include optic hypoplasia which has not been previously documented in this condition.

Neonatal isoimmune thrombocytopenic purpura accounts for 20% of cases of thrombocytopenia in the newborn. Two per cent of women are platelet antibody $A_1$ negative and therefore at risk of an affected pregnancy.[1]

The disease has a mortality of 10–14%[1] and haemorrhagic complications are common. Intracerebral lesions are the main cause of mortality and serious morbidity. Perinatal haemorrhage is well recognised. More recently the prenatal development of such lesions has been documented.[2–6]

We describe five children with neonatal isoimmune thrombocytopenic purpura and porencephaly as a result of prenatal intracerebral damage.

## Case reports

Details of the five cases are shown in tables 1 and 2. All infants developed skin purpura shortly after delivery and were found to be severely thrombocytopenic. All had proved neonatal isoimmune thrombocytopenic purpura, and other causes of thrombocytopenia were excluded.

### CASE 1

This infant had an intracranial haemorrhage in the immediate prenatal period. After an atraumatic delivery she presented aged 2 hours with evidence of neurological abnormality. Cranial ultrasonography showed two haemorrhagic lesions in the right frontoparietal region. There was central resolution of these lesions, the appearances being consistent with haemorrhage several days previously. Apart from transient neonatal seizures she has had no other neurological or developmental problems.

### CASES 2–5

Cases 2–5 present a different picture. Despite severe thrombocytopenia, none had evidence of a perinatal intracranial bleed. All have subsequently presented with serious neurological problems, and a characteristic clinical picture. This consists of porencephaly with or without communicating hydrocephalus, visual impairment with optic hypoplasia, mental handicap, and a variable degree of cerebral palsy. All must have had a prenatal intracerebral vascular event.

Case 5 is of particular interest as the diagnosis of neonatal isoimmune thrombocytopenic purpura was made retrospectively when he was 10 years old. He had neonatal thrombocytopenia of unknown aetiology, and later presented with visual impairment. He had had the characteristic features described above, and we confirmed the diagnosis of neonatal isoimmune thrombocytopenic purpura serologically.

## Discussion

The recognition that intracerebral lesions may occur prenatally in patients with neonatal isoimmune thrombocytopenic purpura has important implications for the further understanding of this condition and for the management of affected pregnancies. Though a number of such cases have now been reported there is no information regarding the incidence, mechanism, and neurological consequences of these lesions.

We have described five infants with neonatal isoimmune thrombocytopenic purpura and porencephaly resulting from prenatal damage. One had an intracranial haemorrhage in the immediate prenatal period. In the other four, severe neurological damage was the result of an intracerebral event that occurred earlier in pregnancy. These earlier lesions give rise to a characteristic pattern of neurological abnormality including optic hypoplasia, which has not previously been described in this disease. Interestingly, one previous case report of congenital porencephaly in two siblings with neonatal isoimmune thrombocytopenic purpura documents similar features, although they describe optic atrophy rather than optic hypoplasia.[6] Examination of our patients clearly indicated that the optic nerves were hypoplastic rather than simply atrophic. The presence of optic hypoplasia is difficult to explain as the result of a

Table 1 *Neonatal data*

| | *Case 1* | *Case 2* | *Case 3* | *Case 4* | *Case 5* |
|---|---|---|---|---|---|
| Maternal and family history | Aged 30, parity 1+0<br>Sibling well | Aged 27, parity 0+1 | Aged 25, parity 1+0<br>Smoker<br>Sibling well | Aged 25, parity 1+0<br>Sibling well | Aged 22, parity 1+0<br>Sibling died age 7 hours – hydrocephalus |
| Obstetric problems | Reduced fetal movements from 35 weeks<br>High blood pressure | None | Intrauterine growth retardation from 32 weeks | None | None |
| Method of delivery | Elective caesarean section | Emergency caesarean section | Spontaneous vertex delivery | Spontaneous vertex delivery | Forceps delivery |
| Birth weight | 3200 g | 3100 g | 2400 g | 2900 g | 3000 g |
| Resuscitation required | None | None | None | None | None |
| Neonatal problems | Petechiae, jittery, seizures | Petechiae | Petechiae, gastric bleeding | Petechiae | Petechiae |
| Initial platelet count | $<10\times10^9/l$ | $10\times10^9/l$ | $7\times10^9/l$ | $10\times10^9/l$ | $8\times10^9/l$ |
| Platelet typing | Mother platelet antibody $A_1$ negative<br>Father platelet antibody $A_1$ positive | Not done | Not done | Not done | Mother platelet antibody $A_1$ negative<br>Child platelet antibody $A_1$ positive |
| Maternal platelet specific antibodies | Positive | Positive | Positive | Positive | Positive |
| Treatment | Exchange transfusion, washed maternal platelets infusion, intravenous immunoglobulin | Exchange transfusion, washed maternal platelets infusion | Donor platelets | None | None |
| Time taken for platelet count to become normal | 24 Hours | 5 Days | 7 Days | 7 Days | 7 Days |
| Neonatal cranial ultrasound findings | Two haemorrhages in right frontoparietal regions | Not done | Large left occipital cyst | Not done | Not done |

Table 2 *Follow up data*

| | *Case 1* | *Case 2* | *Case 3* | *Case 4* | *Case 5* |
|---|---|---|---|---|---|
| Presentation | Routine follow up | Age 2 months<br>Visually unresponsive | Age 2 months<br>Visually unresponsive | Age 6 weeks<br>Hydrocephalus | Age 5 months<br>Visually unresponsive |
| Neurological features | Normal | Visual handicap, spastic diparesis, mental handicap, seizures | Visual handicap, spastic diparesis, mental handicap feeding problems | Visual handicap, spastic quadriplegia, mental handicap, seizures | Visual handicap, spastic diparesis, mental handicap, language delay |
| Ophthalmological features | Normal | Optic hypoplasia, visual evoked responses delayed, electroretinogram normal | Optic hypoplasia, visual evoked responses absent, electroretinogram normal | Optic hypoplasia, visual evoked responses delayed, electroretinogram normal | Optic hypoplasia, visual evoked responses absent, electroretinogram normal |
| Cranial ultrasound findings | Right frontoparietal porencephalic cysts | Left temporal and right occipital porencephalic cysts | Left temporal and cerebellar porencephalic cysts | Massive hydrocephalus and left parietal porencephalic cyst | Not done |
| Computed tomographic findings | Not done | Above with communicating hydrocephalus | Above with communicating hydrocephalus | Not done | Right occipital porencephalic cyst |

haemorrhagic lesion, and the possibility that the primary event may have been ischaemic or thromboembolic requires investigation.

We suggest that intracerebral damage in neonatal isoimmune thrombocytopenic purpura may arise in three different ways. Perinatal haemorrhage may occur as a result of birth trauma. Spontaneous haemorrhage may occur prenatally secondary to severe thrombocytopenia (as in case 1). Finally, earlier prenatal lesions may occur giving rise to the neurological features we have described.

The relative incidence of these lesions is unknown; our experience with five cases suggests that prenatal lesions may be more common than previously thought. Further investigation of the mechanism of the earlier prenatal lesions is required as there are important implications for obstetric management. Regular antenatal ultrasound screening in pregnancies thought to be affected may give further information about the nature and timing of events.

Because the purpura is transient, neonatal isoimmune thrombocytopenic purpura may remain undiagnosed in the neonatal period. Some unexplained cases of porencephaly may therefore be the result of prenatal damage in neonatal isoimmune thrombocytopenic purpura (case 5). We looked at a further five children with unexplained porencephaly and carried out platelet typing of mother and child; in no case was there evidence of platelet incompatibility. Nevertheless, neonatal isoimmune thrombocytopenic purpura should be considered as a possible diagnosis in unexplained porencephaly, particularly if it is associated with optic hypoplasia.

In conclusion, prenatal intracerebral lesions occur in association with neonatal isoimmune thrombocytopenic purpura and give rise to a characteristic pattern of neurological abnormality, including optic hypoplasia. Further clarification of the mechanism of these lesions is required.

We thank Dr R Crawford and the Blood Transfusion Service, Law Hospital for their help.

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# Flecainide toxicity

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SUMMARY Flecainide toxicity occurred in an infant being treated for refractory atrioventricular re-entry tachycardia. Ventricular tachycardia developed when dextrose was substituted for milk feeds. We believe that milk was interfering with the absorption of flecainide, and so a high serum concentration developed when milk feeds were stopped.

Flecainide acetate is a comparatively new drug for the treatment of supraventricular and ventricular arrhythmias. Early clinical experience in infants and children has shown that it is effective and well tolerated.[1 2]

## Case report

A baby boy was born at 34 weeks' gestation after an apparently uncomplicated pregnancy. He was hydropic at birth, weighing 3100 g (>90th centile). Resuscitation with endotracheal intubation was required, and mechanical ventilation was continued for three days. After extubation he remained cyanosed and a hyperoxic test confirmed the presence of an appreciable right to left shunt. Standard investigations did not identify a cause for the hydrops fetalis, and he was referred for cardiological assessment.

On transfer to our hospital at 6 days of age he weighed 2100 g and was no longer hydropic. He appeared cyanosed on 30% oxygen, and was mildly tachypnoeic. There was a grade 2/6 midsystolic murmur, maximal at the left fourth intercostal space. The liver was palpable 3 cm, and the spleen 1 cm, below the costal margin.

The electrocardiogram showed sinus rhythm with no evidence of pre-excitation. A radiograph of the chest showed mild cardiomegaly. Cross sectional echocardiography identified an atrial septal defect, with dominant right to left shunting on contrast and Doppler examination.

The pulmonary venous connection was uncertain so cardiac catheterisation was carried out to exclude total anomalous pulmonary venous connection. A pulmonary arteriogram, however, did establish that the pulmonary veins connected normally to the left atrium. There was appreciable pulmonary hypertension and a right to left shunt at atrial level. It is likely that this was associated with persistent pulmonary hypertension of the newborn.

Cardiac catheterisation was complicated by an episode of supraventricular tachycardia. Direct current cardioversion restored sinus rhythm but several further episodes of tachycardia occurred during the next 24 hours. An electrocardiogram taken during an episode of tachycardia showed the features of atrioventricular re-entry tachycardia. The tachycardia was initially treated by direct current cardioversion and digitalisation, but as the episodes continued flecainide (0·5–2·0 mg/kg) was given intravenously. Oral flecainide was started at a dose of 2 mg/kg in divided doses, and increased while serum concentrations were closely monitored. There was a reduction in the frequency of the episodes of tachycardia as the oral dose of flecainide was increased over a period of two to three weeks. It was noted that a high dose of flecainide was required to gain control of the tachycardia and achieve adequate serum concentrations. The normal recommended dose of flecainide is 2–10 mg/kg in divided doses, but in this patient a total dose of 30 mg/kg did not completely control the tachycardia.

It was suspected that inadequate absorption might account for the poor clinical response, as the tachycardia responded consistently to flecainide given intravenously. To assess this, the serum flecainide concentration was measured two, five, and eight hours after 25 mg of flecainide had been given orally (table). The dose at the time was 25 mg every eight hours (30 mg/kg/day). As the serum concentrations were in the lower part of the reference range, the dose was increased further to 25 mg every six hours (40 mg/kg/day). This abolished the tachycardia for eight days, but there was concern about the high dose required.

Table 1 *Serum flecainide concentrations*

| *Dose of flecainide (mg)* | *Serum flecainide concentrations (µg/l)* after administration (hours)* | | |
|---|---|---|---|
| | *2* | *5* | *8* |
| 25 mg Orally every eight hours (30 mg/kg/day) with milk feeds | 188 | 203 | 519 |
| 25 mg Orally every six hours (40 mg/kg/day) with milk feeds | 990 | — | — |
| 25 mg Orally every six hours (40 mg/kg/day) dextrose feeds only for 24 hours | 1824 | — | — |

*Reference range 400–1000 µg/l.

It was considered possible that milk might be interfering with absorption of flecainide as there was no clinical evidence of malabsorption. This was evaluated by measuring serum flecainide concentrations before and after a 24 hour period of receiving 5% glucose feeds alone (see table). At the end of the 24 hour period he developed ventricular tachycardia. This was present intermittently for the next 60 minutes, but as the patient remained haemodynamically stable no additional treatment was given. The oral flecainide was stopped and milk feeds restarted.

The supraventricular tachycardia recurred 24 hours after the flecainide had been stopped. Treatment with a combination of digoxin and propranolol, and digoxin and disopyramide, was unsuccessful. Eventually he was given amiodarone orally (3 mg/kg three times daily) and when therapeutic serum concentrations were achieved the tachycardia was controlled. During six months of outpatient follow up, he has remained free of tachycardia.

## Discussion

This case shows that milk may interfere with the absorption of flecainide given orally in early infancy, and it is possible for flecainide toxicity to occur on withdrawal of milk feeding. Clinical experience in the use of flecainide in the management of childhood tachyarrhythmias is increasing. There is, however, little information on its use in infancy. The pharmacology of flecainide has been studied in adults[3] and extrapolation to infancy may not be accurate.

Flecainide has a proarrhythmic effect and this may occur within the 'therapeutic range'.[4 5] Ventricular tachycardia has previously been noted with serum concentrations of greater than 1000 μg/l, and occasionally during intravenous administration.[1] This patient developed ventricular tachycardia when a toxic serum flecainide concentration was achieved. It is likely that the ventricular tachycardia was a direct result of that serum concentration. The occurrence of ventricular tachycardia is of concern because of the association between sudden death and such arrhythmias.

Many cardiac units are using flecainide for first or second line treatment of supraventricular tachycardia, particularly in overt Wolff-Parkinson-White syndrome. Milk has not been reported to interfere with flecainide absorption in other children, but Wren and Campbell noted one patient (1 year old) who required a large oral dose (22·5 mg/kg/day) to achieve a therapeutic serum concentration.[6] It is possible that this may be a common phenomenon and merits further investigation. It becomes of particular importance in early infancy when the diet is milk alone. We recommend that milk fed infants on high doses of flecainide should have the dose reduced when milk is reduced or stopped—for example, during an attack of gastroenteritis, or when weaning. Close monitoring of plasma concentrations is likely to be helpful in the management of such patients.

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# Phycomycotic abscesses in a preterm infant

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SUMMARY We report a case of neonatal infection with rhizopus, one of the Mucoraceae family. Human infection is rare but the mortality is high without prompt, correct treatment. The infant had a simultaneous candida septicaemia secondary to colonisation of a central venous line. Serial C reactive protein estimations are valuable in monitoring treatment.

Fungal skin abscesses (usually caused by *Candida* spp) are common among preterm babies, especially those receiving intensive care.[1] We describe an abscess caused by an unusual pathogen, rhizopus, which, although well documented as a cause of serious infection in immunocompromised adults and children,[2–4] has rarely been described in the newborn.[3 5] The case also teaches an important lesson about the diagnosis and treatment of infection with multiple organisms.

## Case report

A baby boy was born by emergency caesarean section (because of antepartum haemorrhage) at 26 weeks' gestation, weighing 1100 g. Mild respiratory distress syndrome was diagnosed and the baby was initially managed in headbox oxygen. On the fourth day of life he required positive pressure ventilation and was transferred to the neonatal intensive care unit at this hospital.

On arrival his blood glucose concentration was 28 mmol/l, he had a metabolic acidosis, and was clinically dehydrated. Despite prompt rehydration he developed acute renal failure due to tubular necrosis. Peritoneal dialysis was needed for nine days until his renal function recovered. During dialysis coagulase negative staphylococcal peritonitis developed, but he was successfully treated with a combination of parenteral and intraperitoneal vancomycin. A Broviac catheter for venous access was sited in the internal jugular vein.

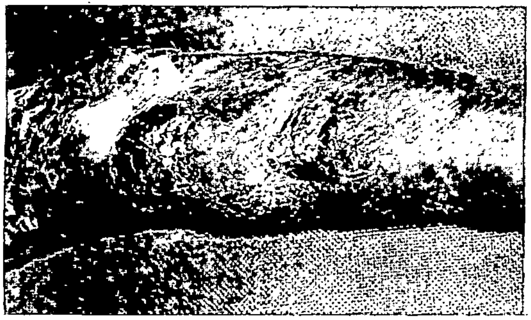

Figure *Multiple abscesses on the baby's arm.*

Two weeks after peritoneal dialysis and despite his seeming well, multiple and rapidly enlarging abscesses developed on his left forearm. They were erythematous, fluctuant and indurated, with necrotic areas at the centre (figure). Investigations to identify the infection were carried out, including serial C reactive protein estimations, venous and arterial blood cultures, urine culture and microscopy, and culture of the tracheal aspirate and of pus from the abscesses. Cloxacillin was given intravenously. All cultures were free from pathogens apart from the pus from the abscesses which, after 48 hours incubation on blood agar at 37°C, grew a 'mucor-like' fungus. This was sensitive to amphotericin B and nystatin, but resistant to flucytosine, miconazole, econazole, and ketoconazole. Further culture of this organism on Sabouraud's medium and malt extract medium confirmed it to be a member of the Mucoraceae group. It was later identified as *Rhizopus* spp by the Regional Mycology Reference Laboratory. In view of the potential virulence of this particular family of fungi[2-6] intravenous amphotericin B was started (despite the previous renal problem) in a dose of 0·25 mg/kg/day that was gradually increased to the full dose of 1 mg/kg/day over a week. The abscesses were surgically drained.

During the following week the baby became unwell with frequent attacks of apnoea and bradycardia that eventually required mechanical ventilation. The liver and spleen gradually enlarged, and the abscesses on the left forearm persisted. A skeletal survey did not show any focus of osteomyelitis, and echocardiography did not show any vegetation. Further investigations to find the cause of the infection were carried out. Microscopy and culture of the cerebrospinal fluid showed no pathogens. Three serial urine cultures contained a yeast, later identified as *Candida parapsilosis,* and both venous and arterial blood cultures grew the same yeast, which was sensitive to amphotericin B, nystatin, flucytosine, ketoconazole, miconazole, and econazole. We gave flucytosine (100 mg/kg/day in four divided doses) and supplemented the antimycotic treatment with a dose of intravenous immunoglobulin (200 mg/kg). The baby showed an initial improvement, the C reactive protein concentration falling from 153 mg/l to 78 mg/l. Subsequently, however, the C reactive protein concentration increased to 270 mg/l, which coincided with further deterioration. Further cultures were carried out, and the Broviac catheter was removed. Although urine cultures now grew no pathogens, blood cultures were still positive for candida and a profuse growth of *Candida parapsilosis* was obtained from the catheter tip. Clinical improvement was rapid thereafter, the C reactive protein concentration falling to 24 mg/l within 10 days.

After four weeks of treatment with full doses of amphotericin B and flucytosine, repeat venous and arterial blood cultures and urine cultures were all free of pathogens. Despite our fears of nephrotoxicity the baby showed no deterioration in renal function as judged by the plasma urea and creatinine concentrations. As is almost invariably the case with treatment with amphotericin B, the potassium intake had to be increased from 2 mmol/kg/day to 5 mmol/kg/day to compensate for the increased tubular losses. The abscesses healed with minimal scarring and the baby continues in good health at the time of writing.

## Discussion

Rhizopus, absidia, and mucor are a group of fungi belonging to the Mucoraceae family, and characterised by broad, branching, and non-septate hyphae. They grow naturally on a variety of organic substances such as bread, fruit, decaying vegetation, and carbohydrate rich substrates. Pathologically they represent an acute and frequently fulminant fungal infection with vascular invasion and tissue infarction as their hallmark.[3-6]

The liberal use of broad spectrum antibiotics and corticosteroids in neonatal practice undoubtedly encourages colonisation with opportunistic pathogens, and the frequent use of indwelling intravenous lines provides plenty of portals of entry. In our unit over 70% of the episodes of septicaemia are caused by coagulase negative staphylococci and we have noticed an increase in the incidence of fungal infections. Infection with rhizopus was nevertheless outside our experience. We presumed that the fungal abscesses developed at a 'tissued drip' site that was later covered with sterile dressing secured by adhesive tape. Most phycomycotic cellulitis occurs after previous injury to the tissues or necrosis,[3-5] and the use of adhesive strapping[3 5] has also been implicated. In debilitated patients, rhizopus infection of the lungs, gastrointestinal tract,[3] sino-orbital region,[2] brain, and skin[4 5] has been reported and the result is often fatal. Although purely cutaneous involvement unassociated with gangrenous cellulitis does seem to have a more favourable outcome, fatal cases have also been reported.[2] The comparatively few reports of successfully treated cases[2 3 4 6] have usually entailed extensive surgical resection in addition to the systemic use of amphotericin B. Our patient was treated with drainage of the abscesses and intravenous amphotericin B. Amphotericin B must be used, as this fungus is often resistant to the more commonly used antifungal agents, which in our case included miconazole, ketoconazole, econazole, and flucytosine. Because of its fulminant pathogenic nature with the ability to produce a rapidly progressive and often fatal gangrenous cellulitis,[4 5] prompt treatment is always essential. Moreover, prolonged use of adhesive strapping on damaged tissue should also be avoided.

The candida septicaemia in this baby was almost certainly secondary to colonisation of the Broviac catheter, but despite the infusion of potent antifungal drugs through the line this focus was not eradicated. The persistent rise in the C reactive protein concentration was a useful indicator of the presence of continuing infection, which was only eradicated after removal of the line.

We conclude that rhizopus infection must be considered as a cause of cutaneous abscess in the newborn and if confirmed must be treated without delay by surgical drainage and parenteral amphotericin B. We have also shown the value of serial measurements of C reactive protein concentrations in monitoring the treatment of systemic fungal infections. Central venous lines should be removed promptly if fungal septicaemia is suspected.

We thank the microbiology department at St James's University Hospital and the Regional Mycology Reference Laboratory at Leeds General Infirmary.

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# A new cardiomyopathy in girls

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SUMMARY A type of cardiomyopathy characterised by isolated severe dilatation of the right heart with right ventricular hypertrophy and absence of cardiac arrhythmias is described in seven patients. Only girls were affected and all except one lived in rural Zimbabwe. Six were under 5 years old. This probably represents a new type of cardiomyopathy.

Cardiomyopathies are uncommon in childhood but all the types seen in the adult population have also been described in children.[1] Their overall contribution to childhood cardiac disease remains largely unknown. This article describes a form of cardiomyopathy that has so far not been described in children.

## Patients and methods

Seven girls between 3 months and 14 years of age were seen over a 22 month period in our paediatric cardiac clinic for assessment of unexplained cardiomegaly or heart failure. Six were under the age of 5 years. All had chest radiographs and a 12 lead electrocardiogram was available in five patients.

Two dimensional echocardiography was performed using a 5 MHz Advanced Technology Laboratory Mark III sector scanner. Standard views were used for evaluation of cardiac anatomy.

## Results

The clinical data on the seven girls are summarised in the table. Four patients presented with dyspnoea due to acute bronchopneumonia and two of these (cases 4 and 6) were in severe respiratory distress. In case 6 this was due to smoke inhalation and mild chest infection. One patient (case 1) was admitted with croup and developed bronchopneumonia and right heart failure two days later. Only two patients (cases 1 and 4) had previous hospital admissions, both for chest infections. The oldest patient, a 13 year old girl, had a history of exertional dyspnoea for two weeks and was initially thought to have rheumatic heart disease. No patient had clinical

Table *Clinical features of seven girls with right heart dilated cardiomyopathy*

| *Case no* | *Age* | *Presenting complaints* | *Cardiothoracic ratio* | *Electrocardiographic features* | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | *Mean QRS axis* | *R V1* | *S V1* | *R V6* (mm) | *S V6* |
| 1 | 1 year 10 months | Croup | 0·60 | −160 | 3 | 7 | 3 | 15 |
| 2 | 14 years | Right heart failure, exertional dyspnoea for 2 weeks | 0·75 | 90 | Low voltage complexes | | | |
| 3 | 12 months | Oedema, cough for 4 months | 0·65 | 140 | 2 | 0 | 3 | 7 |
| 4 | 3 years | Chest infection | 0·77 | 150 | 10 | 0 | 3 | 0 |
| 5 | 9 months | Oedema, chest infection | 0·66 | | Not available | | | |
| 6 | 3 months | Chest infection, smoke injury | 0·65 | | Not available | | | |
| 7 | 2 years 8 months | Oedema, chest infection | 0·65 | 140 | 13 | 1 | 7 | 14 |

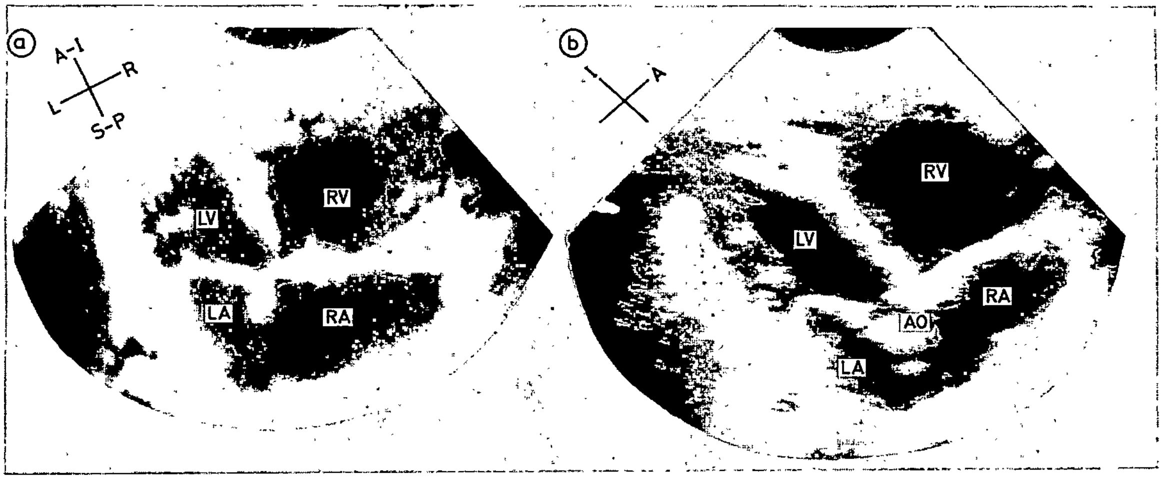

Figure *(a) Apical four chamber view of one of the girls showing a greatly dilated right heart and compressed small left chambers. The interatrial septum can be seen to be fully intact. (b) Two dimensional echocardiogram of one of the girls: the image is midway between apical four chamber and left parasternal long axis view. The aorta can be seen between the left atrium and the dilated right atrium. The right ventricle is very dilated and also hypertrophied and the left ventricle is compressed to a much smaller chamber. A, anterior, AO, aortic root; I, inferior; L, left; LA, left atrium; LV, left ventricle; P, posterior; R, right; RA, right atrium, RV, right ventricle; S, superior.*

evidence of appreciable pulmonary hypertension. The precordium was remarkably quiet and left parasternal impulse was not prominent in any patient. The heart sounds were normal with the exception of one patient (case 7) with a slight accentuation of the pulmonary component of the second sound. A murmur of mild tricuspid regurgitation was present in only one patient (case 4). Right heart failure was present at some stage in all the patients. In cases 1 and 3 peripheral oedema was gross. History and clinical examination did not suggest cardiac arrhythmia in any patient.

The electrocardiogram showed sinus rhythm in all patients. The mean QRS axis ranged from 90–150° in four patients and was superior (−160°) in one. P wave was normal in all. Electrocardiographic evidence of right ventricular hypertrophy was present in three patients. The chest radiograph showed cardiomegaly in all and the most common pulmonary changes were pneumonic infiltrates, but two patients had completely normal lung fields.

The two dimensional echocardiographic features were identical in all the patients. The most striking abnormality was the severe dilatation of the right ventricle and right atrium (figure). The interatrial septum was intact in each case and could be seen bulging into the left atrium, thus reducing its cavity enormously. Pulmonary venous drainage was normal. The dilated right ventricle was slightly to moderately hypertrophied. The interventricular septum was intact and abnormal interventricular septal and ventricular wall motion was not prominent in any of the patients. The atrioventricular valves appeared normal and were normally located. The ventriculoarterial connections were concordant and no persistent ductus arteriosus was present. No patient had pericardial effusion.

## Discussion

Harris and Nghiem defined cardiomyopathy in children as intrinsic disease of the myocardium that is not caused by shunts or valvar disease and subdivided them into primary and secondary types.[1] The seven girls described here fulfil this definition and the cardiomyopathy can be regarded as primary. In children in developing countries the problem of recognition and classification of cardiomyopathies is often made difficult by the frequent occurrence of previously unrecognised rheumatic heart disease, which is quite common, uncorrected long standing congenital heart disease, and lack of adequate facilities and expertise for full investigation of cardiac disease. Many patients who died of cardiac disease will have had no necropsy and in cases where they were carried out the reports are often incomplete and unreliable. As rheumatic heart disease is common in developing countries there is a possibility of it being superimposed on a cardiomyopathy making recognition of the cardiomyopathy even more difficult. Most of the patients described here, however, are outside the usual age range for rheumatic heart disease.

Dilated cardiomyopathy is the commonest type of cardiomyopathy encountered in children and affects both ventricles with more severe involvement of the left side.[2] It has a definite male preponderance and the first cases in children were reported from South Africa.[3] [4] Unlike the classic cases of dilated cardiomyopathy the seven children reported here have isolated right heart involvement. Other important features of these children are the exclusive involvement of girls and also their very young age.

The age of most of the patients would make one suspect congenital heart disease, notably total anomalous pulmonary venous drainage, as the cause of the cardiac problem. Venous drainage was, however, normal in each child and the obligatory atrial septal defect or patent forumen ovale of anomalous venous drainage were absent in all the girls. The possibility of primary pulmonary hypertension was excluded on clinical grounds. The fact that chest infection was common in these children does not necessarily mean left heart involvement as lower respiratory infections are extremely common in children in Zimbabwe and are by far the commonest cause of hospitalisation even in children without cardiac disease.

Only one patient was older than 5 years. The exclusive involvement of girls is unlikely to be a mere coincidence as biventricular dilated cardiomyopathy has been seen in both sexes in our child population. Another interesting and unexplained feature in these patients is the fact that all except the 3 month old infant lived in rural Zimbabwe.

A recent series from Hammersmith hospital reported on 14 cases of dilated cardiomyopathy with involvement of the right ventricle only.[5] There was the usual male predominance in the series which included six children, four boys and two girls, the youngest of whom was 9 years old. The most prominent presenting features of those patients were syncope and cardiac arrhythmias, which were present in 70% of the cases. No patient in the present series had symptoms of cardiac irregularities and history and available electrocardiograms did not show any such disturbances. While there are similarities between the two groups of patients, there are obvious differences so that the children reported here most probably represent a different and new clinical entity.

I am grateful to Miss M Mudzingwa for her excellent secretarial help.

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# Diarrhoea caused by collagenous colitis

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SUMMARY The first case of collagenous colitis in a child with protracted watery diarrhoea and abdominal pain is reported. Small bowel investigations and the macroscopic appearances were normal, but histological examination of the colon showed collagenous colitis. Steroids temporarily relieved the diarrhoea and induced transient dissolution of the subepithelial collagen band.

Colitis in children is normally associated with bloody diarrhoea with mucus, tenesmus, and abdominal pain, and is usually caused by ulcerative colitis or Crohn's disease.[1] Colitis caused by amoeba, campylobacter, antibiotics, food allergy, irradiation, or Hirschsprung's and Behçet's diseases are all uncommon. Recently microscopic and collagenous forms of colitis have been described in adults that cause profuse watery diarrhoea but remarkably occur without blood or mucus; thickening of the basement membrane is typical of this so called, 'collagenous' form.[2 3] As far as we are aware no case has so far been reported in children, and we how report the first one.

## Case report

A boy of 5 years old was referred to our unit with a four and a half year history of recurrent watery diarrhoea and abdominal pain, each episode lasting for about a week. During each episode his bowels opened up to 10 times a day, but he had otherwise grown and developed normally. His weight and height were on the 75th percentile, and between the 25th and the 50th percentiles, respectively. Examination showed no abnormal signs. Routine tests, including complete blood count, analysis of urine, plasma biochemistry, repeated stool culture and examination for parasites, stool chromatography for sugars, sweat chloride excretion, faecal fat excretion, lactose and sucrose tolerance tests, small bowel biopsy, and barium follow through examination, were all normal; erythrocyte sedimentation rate was 29 mm in the first hour. Dietary exclusion of dairy products, eggs, fish, chocolate, sweets, fruit other than apples, and all processed foods, was of no benefit. Colonoscopy and ileoscopy showed no macroscopic abnormalities but histological examination of the biopsy specimens showed pronounced inflammation and thickening of the basement membrane.

### HISTOPATHOLOGY

The initial biopsy specimens of large bowel mucosa were fixed in 10% formalin and embedded in paraffin; sections were then taken from several levels of each block and stained with haematoxylin and eosin, periodic acid-Schiff, van Gieson's, and Congo red. The most striking abnormality was the increase in the thickening of the basement membrane between crypts. This stained pale pink with periodic acid-Schiff, and red with van Gieson's, but did not show amyloid when stained with Congo red. One of us (GK) measured the basement membrane thickness using slides stained with haematoxylin and eosin and a Zeiss calibrated eye piece graticule. The thickness was estimated 30 times on each specimen in 25 adjacent intercrypt areas, and the mean thickness was 5·5 μm (range 3·7–9) (fig 1a). In addition the lamina propria was oedematous with an increased number of plasma cells and lymphocytes, particularly in the upper part of mucosa; there were no crypt abscesses or signs of ulceration.

In order to define the range of basement membrane thickness in children with other diarrhoeal diseases we retrospectively examined 543

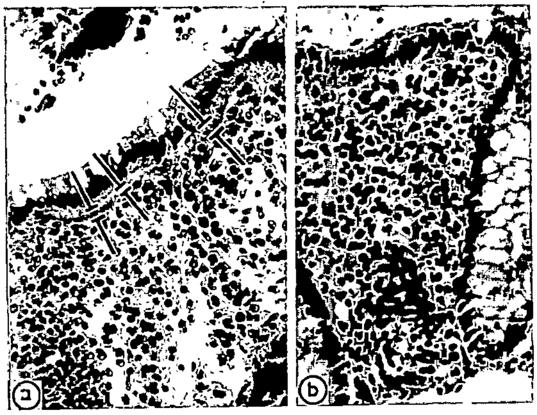

Figure (a): *Rectal biopsy specimen taken before treatment showing prominent collagen band below the surface epithelium (—| |—) that varies from 3·5–9·0 μm thick. Note infiltration by lymphocytes and plasma cells, and oedema of the lamina propria. (Haematoxylin and eosin ×160.)*
*(b) Rectal biopsy specimen taken in remission showing dissolution of the collagen band. Lesser inflammatory changes persist. (Haematoxylin and eosin ×280.)*

specimens of colonic mucosa from 303 children who had undergone colonoscopy for the following diseases: ulcerative colitis (n=161), Crohn's disease (n=16), chronic non-specific colitis (n=80), allergic colitis (n=22), campylobacter colitis (n=11), pseudomembranous colitis (n=1), Hirschsprung's colitis (n=2), and coeliac disease (n=10). Mean (SD) basement membrane thickness in the control biopsy specimens was 1·2 (0·6) μm confirming a highly significant increase in the thickness in the biopsy specimens from the patient (p<0·01).

### RESPONSE TO TREATMENT

Sulphasalazine, cholestyramine, and loperamide each failed to control the diarrhoea, but a six week course of oral prednisolone (1 mg/kg/day) was effective in controlling his symptoms. Repeat examination of a colonic biopsy specimen eight weeks later showed that the collagen deposition was definitely reduced, although a microscopic colitis was still present (fig b). Eight months after the discontinuation of steroid treatment the patient relapsed with profuse watery diarrhoea and abdominal pain. Biopsy specimens from the colonic mucosa again showed subepithelial collagen deposition ranging from 3·0–5·0 μm thick. Steroids relieved the severity of diarrhoea, the stools became less watery, and the abdominal pain disappeared.

## Discussion

Collagenous colitis has previously been described in adults as an uncommon cause of watery diarrhoea, usually accompanied by colicky pain.[3] Barium enema examination, colonoscopy, and laboratory investigations of the chronic diarrhoea are all normal, and the histological hallmark is an abnormally thick band of collagen beneath the colonic epithelium; the cause of the excess collagen deposition is unknown.[3] Lindstrom suggested that the thick collagen band may cause diarrhoea by interfering with water absorption,[3] but perfusion studies would not support this hypothesis.[4] No child with collagenous colitis has been described to our knowledge.

Microscopic colitis is another similar but equally uncommon cause of chronic watery diarrhoea in adults.[2] The diagnosis is based upon macroscopically normal colonic mucosa that shows microscopic mild, uniform, colonic mucosal inflammation.[2] Laboratory investigations of the chronic diarrhoea are also normal. Sanderson *et al* reported the first paediatric patient,[5] and recently Levine *et al* suggested that microscopic colitis and collagenous colitis might be variants of the same disease.[6] Both have the same clinical presentation, and radiographs and endoscopy of the large bowel, as well as routine laboratory tests, show no abnormalities. Indeed, the only histopathological distinction is the presence of subepithelial collagen deposition, and our observations are consistent with the suggestion that microscopic colitis might precede or follow collagenous colitis.[2 3 6]

Our case, therefore, confirms the diagnostic value of colonic biopsy in children with diarrhoea.[5] We also confirm that collagenous colitis does occur in children, and suggest that basement membrane thickening may parallel the clinical activity of colitis. Furthermore, though steroids may be of some symptomatic benefit, they do not seem to alter the natural history of the disease.

We thank Dr IW Booth for his help with this manuscript.

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# Effect of fever on recurrence rate of febrile convulsions

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SUMMARY We studied 154 children admitted consecutively with their first febrile convulsion to assess the influence of the temperature on the recurrence rate of convulsions. Those with temperatures of 40°C or more were nine times less likely to have subsequent convulsions than those with temperatures of 38–38·9°C.

Factors associated with increased risk of recurrence of febrile convulsions are: the first febrile convulsion occurring before 12 months of age, a history of febrile convulsions in first degree relatives, and the presence of associated complex features of febrile convulsions.[1] Little information is available about factors associated with a reduced risk of recurrences. In a previous retrospective study with a limited number of children[2] we suggested that a high temperature during the initial febrile convulsions was associated with a decreased incidence of recurrent febrile convulsions. We have expanded the study by including 79 further children prospectively studied since January 1982.

## Patients and methods

All children who presented to the paediatric department of this hospital with their first febrile convulsion between January 1980 and February 1986 were included in the study.

The study group comprised 173 children (91 boys and 82 girls). All except four had been born here, so their earlier records were available. Four infants were of low birth weight but had made normal neonatal progress, and the remainder were born at full term with birth weights within the normal range; they had also made uncomplicated postnatal progress.

A febrile convulsion was defined as a generalised convulsion associated with a temperature of more than 38°C that occurred in a child aged 6 months to 5 years who had no pre-existing evidence of neurological abnormalities. All the children were managed consistently according to a routine protocol aimed at reducing body temperature. Paracetamol (10 mg/kg, every four hours) was prescribed for temperatures of over 38·5°C. The rectal temperature was recorded on admission and then every four hours. Routine investigations included a full blood count and cultures from throat, urine, and stool. Blood culture, chest radiograph, and lumbar puncture were not performed unless there were clinical indications. Antibiotics were used if there was evidence suggesting bacterial infection.

The children were divided into three groups according to the severity of the fever recorded on presentation to hospital. Group 1 had temperatures >40°C, group 2, 39–39·9°C, and group 3, 38–38·9°C.

Fifteen children were lost to follow up. Four children subsequently developed afebrile convulsions and were withdrawn from the study. The remaining 154 children were reviewed at three monthly intervals for a mean of 40 months (range 27 to 96).

## Results

The groups were comparable with regard to age, sex, and family history of febrile convulsions.

Bacterial infection occurred in 24 patients (16%), 12 in group 1, 10 in group 2, and two in group 3. These infections were tonsillitis (n=2), shigella enteritis (n=4), salmonella enteritis (n=6), otitis media (n=8), pneumonia (n=2), and urinary tract infections (n=2). Antibiotics were not used to treat salmonella and shigella enteritis.

The recurrence rates of febrile convulsions are shown in the table. None of the 11 children who had their initial febrile convulsions after the age of 30 months had a recurrence. The average number of

Table *Recurrence of febrile convulsions in children with temperatures of ≥40°C (group 1), 39–39·9°C (group 2), and 38–38·9°C (group 3)*

| *Age range (months)* | *Group* | *Total No* | *Male:female ratio* | *No (%) with recurrent convulsions* | *p Value* |
|---|---|---|---|---|---|
| 6–18 | 1 | 49 | 26:23 | 4 (8) | <0·001* |
| | 2 | 32 | 15:17 | 19 (59) | |
| | 3 | 13 | 8:5 | 10 (77) | |
| 19–30 | 1 | 22 | 14:8 | 4 (18) | <0·01** |
| | 2 | 21 | 10:11 | 5 (24) | |
| | 3 | 6 | 1:5 | 5 (83) | |
| >30 | 1 | 6 | 4:2 | 0 | |
| | 2 | 4 | 3:1 | 0 | |
| | 3 | 1 | 0:1 | 0 | |
| Total | | 154 | 81:73 | 47 (31) | |

*Group 1 compared with both group 2 and group 3; **group 1 compared with group 2, and group 2 compared with group 3.

recurrences was 3·0 (range 2–7), and these occurred between one and 22 months after the original episode.

## Discussion

Our results suggest that the recurrence rates of febrile convulsions were significantly greater in infants aged 6–18 months in whom the initial febrile convulsions had been associated with a lower temperature. The rate of recurrence was over nine times higher in infants who had the lowest fever, 38–38·9°C (77% compared with 8%) and over seven times higher in infants with temperatures of 39–39·9°C (59% compared with 8%). For infants aged 19–30 months, the recurrence rate was also higher with the lesser degree of fever (table).

It remains unclear why it is rare for a child to develop repeated convulsions during the same febrile illness or subsequently when exposed to similar or higher temperatures. Although the children who were admitted with febrile convulsions usually continued with spikes of fever for a few days, repeated convulsions occurred in only four children (3%). Previous publications[3] have reported that 50% of the recurrences occur within six months of the initial convulsion. Our results were similar, 28 out of 47 (60%) having had recurrences within six months. Recurrences within one month were rare (four of 47=9%), and only 10 (21%) had their recurrences within three months, although most of the children (82%) had febrile illnesses during this period.

It is possible that the central nervous system enters a refractory phase after febrile convulsions that protects the patient from a further febrile convulsion, and this phase is longer the higher the temperature at the time of the initial convulsion. The reason for that is not clear. During the past 20 years considerable data have accumulated suggesting that fever is beneficial to the infected host. More studies on fever in specific diseases are necessary to determine if fever alone is beneficial, harmful, or without effect.[4] In febrile convulsions it is unlikely that the fever itself or the rate of rise of body temperature are the only precipitating factors. There may be an invasion of virus into the central nervous system in a vulnerable child.[5] Such a virus may trigger antibody response, which protects against reinfection and further febrile convulsion. It is also now well established that fever (by enhancing human host defences) produces various substances that are collectively termed interleukin 1.[6] Interleukin 1 is known to be pyrogenic and a lymphocyte stimulator. It follows that the amnastic response of the lymphocyte may correlate with the degree of fever and can therefore protect the host from reinfection. In brain tissue the interleukin 1 produced by astrocytes may contribute to such an immunological response within the central nervous system, and play a part in protecting the patient from further convulsions.

Our data suggest that the degree of fever at the time of the initial febrile convulsions might be a useful prognostic indicator of the risk of recurrence of febrile convulsions.

We thank Dr A Mowat, King's College Hospital, London, and Dr J Wilson, the Hospital for Sick Children, Great Ormond Street, London, for their advice in preparing this manuscript.

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# Infantile botulism

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SUMMARY A 4 month old boy presented with respiratory difficulty and hypotonia. *Clostridium botulinum* and its toxin were isolated from his faeces and he had electromyographic changes typical of infantile botulism. This is only the second case in the United Kingdom: unfamiliarity with the presentation could result in misdiagnosis.

Infantile botulism results from the production of *Clostridium botulinum* toxin in the infant gut. It was first recognised in 1976[1] and more than 600 cases have been reported since, most of them from North America. Only one previous case has been reported in the United Kingdom, which was caused by *C botulinum* type A.[2] We describe a second case, and only the third ever reported caused by *C botulinum* producing toxins B and F.

## Case report

The patient was a boy aged 4 months. He was born at full term after a normal pregnancy, was breast fed from birth, and growth and development were normal. He was given his first doses of diphtheria, tetanus, pertussis, and oral poliomyelitis vaccines three weeks before admission to hospital. Baby rice and rusks were added to his diet about one week later because of 'constipation' attributed by his parents to underfeeding, and for the week before admission he had had profuse rhinorrhoea.

Twenty four hours before admission he had difficulty feeding, and was less active than normal. By the next day he was 'floppy' and in respiratory distress, and on admission there was profound generalised hypotonia with bilateral ptosis, impassive facies, reduced tendon reflexes, a poor gag reflex, and pharyngeal pooling. Spontaneous movements were few but he seemed visually alert and showed definite withdrawal from pain. Physical examination otherwise yielded normal results.

Haematological measurements were unremarkable, and normal biochemical results included blood urea, electrolytes, creatinine, glucose, and lead concentrations, and normal aspartate transaminase activity. Urinary screening for drugs, porphyrins, and other metabolic abnormalities gave normal results. Examination of the cerebrospinal fluid on admission showed no cells, a normal glucose concentration, protein concentration of 0·19 g/l, and no growth on culture for bacteria or viruses. A rhinovirus was isolated from two separate nasopharyngeal aspirates, and poliovirus type 3 (thought to be the vaccine strain) from his stool. No clinical change was observed after an intravenous dose of edrophonium (0·1 mg/kg).

Electrophysiological testing within 24 hours of admission showed normal sensory nerve conduction and normal motor conduction velocities, but a greatly reduced amplitude of motor action potentials. Tetanic stimulation caused reproducible incrementation but there was no post-tetanic facilitation. An electroencephalogram on admission showed generalised excess high amplitude slow wave activity. This non-specific abnormality was rather more pronounced a week later, but thereafter returned to normal.

The patient was initially treated with netilmicin and ampicillin; subsequent management was supportive. Two days after admission (day four of the illness) intermittent positive pressure ventilation was required. Although he retained some respiratory movements throughout his illness he showed profound hypotonia, losing pupillary reflexes for several days.

The child began to show definite improvement by day 18 and was extubated on day 24. Improvement was then rapid, his air of alertness progressing in advance of his muscular strength. He was discharged on day 45, able to feed from a bottle. He still had considerable hypotonia but was responsive, babbled, and was able to grasp toys. This improvement has continued.

Faecal specimens were sent to the Food Hygiene Laboratory, Central Public Health Laboratory, London. Mouse neutralisation tests showed *C botulinum* toxin in a stool specimen from day 9. *C botulinum* producing toxins B and F were later isolated. Toxin was not detected in his serum.

## Discussion

Infantile botulism presents with characteristic signs:

the first is usually constipation and poor feeding, progressing to a more profound hypotonia with loss of head control, a weak cry, cranial nerve palsies, and pharyngeal pooling. Severity varies from sudden infant death to mild cases presenting with hypotonia and failure to thrive. Asymptomatic carriers have been described. Differential diagnoses include septicaemia, meningitis, drug or chemical poisoning, metabolic imbalance, and neuromuscular disturbances such as Guillain-Barré syndrome, myasthenia gravis, and poliomyelitis.

The diagnosis is confirmed by a typical electromyographic pattern and from the isolation of *C botulinum* and usually of its toxin from faeces, but in this case the picture was complicated by a recent upper respiratory infection, immunisation, and the presence of type 3 poliovirus in the child's stool. Because the peak incidence of infantile botulism occurs between 2 and 4 months of age, this fortuitous association with immunisation is common in the United States.

Our case showed typical clinical and electromyographic features. The presence of *C botulinum* and its toxin in his stool confirmed the clinical diagnosis. Other diagnoses, particularly paralytic poliomyelitis and Guillain-Barré syndrome, were rejected because of the absence of fever, normal cerebrospinal fluid, the absence of sensory abnormalities, and the extent and speed of his recovery.

Electrophysiological testing provides a useful guide to the diagnosis. If there are normal sensory and motor nerve conduction velocities on repeated examinations, it helps to exclude primary nerve disorders such as the Guillain-Barré syndrome. Of greater help are the electromyographic findings. Botulinum toxin blocks the release of acetylcholine from the neuromuscular junction. The motor action potentials are characteristically greatly reduced in amplitude and decrement is seen on low amplitude repetitive stimulation (1–5/s). This phenomenon is seen in many conditions causing defects in neuromuscular transmission. Repetitive stimulation at fast rates (50/s), however, causes a progressive increment, and occasionally (but not in the present case) post-tetanic potentiation. These changes are similar to but less severe than those seen in the Eaton-Lambert syndrome.

This is the second case of infantile botulism to be described in the United Kingdom—a disease incidence much lower than that reported in the United States. One possible explanation of this difference is the variation in the number of *C botulinum* spores in the environment, which may be reflected in the likelihood of contamination of food or dust. There was no history of building locally, but there had been recent digging in a road near the parent's house. Other workers have noted an association between the onset of illness and an increase in dusty conditions.[3] No environmental specimens were examined in this case. Honey has been implicated in several cases from the United States, but a survey of honey in the United Kingdom did not report any contamination.[4] There was no history of the child having eaten honey, and the mother's diet was normal. As in our case other authors have noted an association between the onset of illness and the introduction of solid foods to previously breast fed infants.[3] It has been proposed that formula fed infants may experience a more severe form of the illness and present as sudden infant death syndrome; this, however, has not been proved.

The isolation of a *C botulinum* strain producing two serologically distinct neurotoxins is rare. In this case type B and F toxins were produced predominantly when the isolate was incubated at 37°C and 30°C, respectively. Only two cases of infantile botulism attributed to a strain producing toxins B and F have been previously reported (C Hatheway, personal communication).[5]

The diagnosis of infantile botulism requires laboratory confirmation, and will not be made if the illness is not considered. It is possible that cases of infantile botulism are currently being missed in the United Kingdom, and in view of this second report we suggest that infantile botulism should be actively entertained in the differential diagnosis of any acutely 'floppy' baby.

In suspected cases of infantile botulism about 5–10 g of faeces and 2–3 ml of serum should be sent to the Food Hygiene Laboratory, Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT.

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# Meningitis in the newborn – a 14 year review

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SUMMARY A 14 year review of meningitis in babies showed that overall mortality and survival without handicap has not improved. The failure to improve the prognosis of these babies during a period when overall perinatal mortality fell rapidly is because smaller babies are being affected and different organisms are being cultured.

Neonatal meningitis remains a serious problem with a high mortality rate of about 60%.[1] In no other age group is meningitis more common than in the newborn with an incidence of 0·4/1000 live births.[2]

There are few up to date reviews of neonatal meningitis and so we report our experience over the past 14 years.

## Patients and methods

From January 1973 to December 1986, 41 babies with meningitis were treated in the newborn nursery of the Royal Maternity Hospital (RMH), Belfast. These included three babies who were more than 28 days of age and therefore did not meet the strict criteria of 'neonatal meningitis'. Three babies with myelomeningocele were not included. A diagnosis of neonatal meningitis was made if organisms were cultured from the cerebrospinal fluid. In cases in which the cerebrospinal fluid was sterile we used the criteria of Bush who suggested that pleocytosis with a cell count of more than 100/mm$^3$ is diagnostic of meningitis even in the absence of a positive culture.[3] If the cerebrospinal fluid was blood stained, a white cell count exceeding normal haemic proportions by 100 cells/mm$^3$ was accepted as diagnostic of meningitis. Analysis of cerebrospinal fluid in our laboratory was done by Gram stains and standard bacteriological methods of culture and inoculation.

Treatment of meningitis was with combinations of antibiotics given intravenously, the most common being an aminoglycoside with benzylpenicillin, chloramphenicol, or a cephalosporin. In addition about half the babies were treated with intrathecal gentamicin. A standard dose of 1 mg intrathecal gentamicin was given daily for one to five days.

A complete neurological examination and Denver screening test was carried out on all surviving infants when they were 2 years of age or older by consultant paediatricians.

Statistical analysis was by Student's *t* test for comparisons of means, and $\chi^2$ or Fisher's exact test for comparisons of proportions; Fisher's exact test was used for small numbers.

## Results

### INCIDENCE AND RISK FACTORS

Over the 14 year period 44 277 babies were born in the Royal Maternity Hospital, Belfast, of whom 24 developed meningitis, giving an incidence of 0·54/1000 live births. The incidence has fallen progressively from 1979 (1·11/1000 live births) to 0·56 in 1984, with no cases in 1985 or 1986. In addition, 17 babies born at other hospitals also had meningitis treated at RMH. There were 19 boys and 22 girls, mean (SD) birth weight was 1823 (700) g, and mean gestational age was 32·2 (3·7) weeks. Antenatal risk factors were rupture of the membranes for longer than 24 hours (n=8) and maternal infection (n=6).

Table *Organisms from cerebrospinal fluid and blood*

| | *1973–1979 (n=19)* | | *1980–1986 (n=22)* | |
|---|---|---|---|---|
| | *Cerebrospinal fluid* | *Blood* | *Cerebrospinal fluid* | *Blood* |
| *E coli* | 8 | 5 | 7 | 6 |
| *Staphylococcus aureus* | 3 | 3 | 3 | 3 |
| *Streptococcus viridans* | 1 | 0 | 0 | 0 |
| Group B streptococcus | 1 | 0 | 1 | 1 |
| *C albicans* | 0 | 0 | 2 | 0 |
| Others* | 0 | 0 | 3 | 3 |

*Includes one with *Proteus mirabilis*, one with *Serratia marcescens*, and one with *Enterobacter cloacae*.

Five mothers had urinary tract infections and one had appendicitis.

PRESENTATION

Signs and symptoms were vague in most cases, with apnoea being the most common. In only four cases was a full or bulging fontanelle noted, and in no case was fever recorded. In five infants the diagnosis was made at necropsy. Median age at presentation was 9 days (range 1–57).

ANALYSIS OF CEREBROSPINAL FLUID

Twenty nine babies had bacteria cultured from the cerebrospinal fluid, and in 21 organisms were also cultured from the blood. The commonest organism was *Escherichia coli* (table). In 12 babies cerebrospinal fluid was sterile on culture, but they all had a pleocytosis of more than $100/mm^3$, and in four of the 12 *E coli* was grown from the blood.

OUTCOME

Twenty babies died (49%), and only 13 (32%) survived without handicap. The median age at death was 17 days (range 2–45). Of the eight babies with handicaps, three have hydrocephalus, three spastic tetraplegia, and two monoplegia. Babies weighing less than 2500 g at birth had a significantly higher mortality rate compared with those who had weighed more than 2500 g (figure).

Only two factors were associated with poor outcome: low birth weight ($p<0{\cdot}05$) and a positive cerebrospinal fluid culture ($p<0{\cdot}01$). There was no difference in outcome between babies born in the hospital and those transferred from other hospitals.

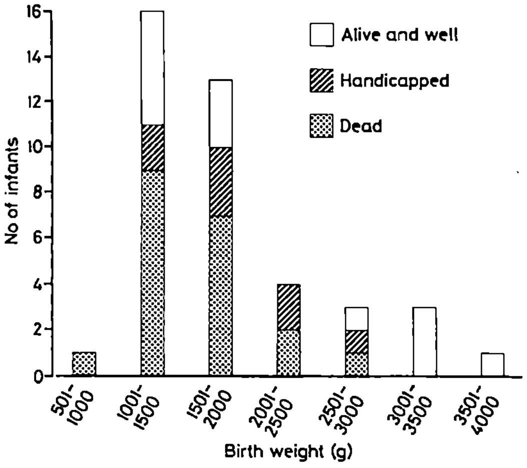

Figure *Outcome of infants and birth weight.*

A comparison of risk factors and outcome in babies born up to 1979 and those born after 1979 showed that the latter were significantly lighter and less mature than the former; mean (SD) birth weights were 1584 (563) g and 2101 (753) g, respectively ($p<0{\cdot}05$). Although the mortality rate was higher in the more recent period ($n=12$, 54%, compared with $n=8$, 42% in the preceding period), survival without handicap was identical during the two periods at 32% (seven and six babies, respectively).

## Discussion

Coliforms remain the single commonest organism causing meningitis in the neonatal period.[4] Outcome remains poor, despite the increased availability of more potent antibiotics and the ability to give them intrathecally.[5] In recent years, we have noted the appearance of more unusual organisms—for example, *Candida albicans* and *Serratia marcescens*. This probably reflects overall changes in the patient population, with smaller babies being treated for longer periods with intensive care including invasive procedures, parenteral nutrition, and the use of broad spectrum antibiotics.[6] The outcome for the babies with more unusual organisms was uniformly fatal.

The low incidence of meningitis caused by group B streptococcus may be possibly explained by late presentation to other hospitals.

What is clear from this study is that the rates of mortality and survival without disability are largely unchanged from earlier years, and in this respect one cannot ignore the importance of the treatment of smaller babies and the emergence of different organisms in more recent years. With this change in epidemiology, improved methods of diagnosis and management are needed.

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## *Personal practice*

# Organ donation

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Transplantation is now an established form of treatment for organ failure in childhood. Much has been published on the outcome and management of children with organ transplants, the ethical issues have been widely discussed, and the criteria for the diagnosis of brain death have been established. Most transplanted organs are taken from donors who are brain dead but have a circulation and are being mechanically ventilated, and recent publicity has drawn attention to a lack of such donors. Staff working on intensive care units, particularly doctors, have been repeatedly criticised for their lukewarm attitude towards organ donation and their failure to ask relatives of patients for permission to remove organs for transplantation. This criticism is primarily directed at those caring for sick adults but the shortage of organs for donation applies equally to children. The current debate is centred on ways of increasing the number of organs donated; by publicity, by obliging staff to ask relatives about organ donation (required request), or by an opting out scheme to replace the present system of organ donor cards. Surprisingly, there is no information to guide doctors caring for a child who is a potential organ donor. It is assumed that organ donation is a straight forward procedure once brain death has been diagnosed and parental consent has been obtained, but this is not so.

An unhappy experience in our own unit recently led to a series of discussions on the subject of organ donation that involved medical and nursing staff and the local transplant team. It became clear that many interests need to be considered, particularly if multiple organ donation is being contemplated: the child and his family, the nurses and doctors responsible for the child's care, the transplant team and its coordinator, the various transplant centres (national and international), the coroner, the pathologist, and the local hospital services such as blood transfusion, theatre, and the mortuary. It was also clear that our unhappiness and unease that had resulted from previous attempts at organ donation arose from divided loyalties and blurring of responsibilities. A series of guidelines were agreed upon and drawn up for future occasions and have since been put into practice successfully. They are presented here in the hope that other paediatricians might find them useful. A few parochial details have been omitted but otherwise the guidelines are applicable to any children's department with intensive care facilities.

### The case for transplantation in children

Renal transplantation is now well accepted as the treatment goal for children with end stage renal failure, even for infants less than one year of age. Success rates have continued to improve as experience increases and newer immunosuppressive agents such as cyclosporin are used. Actuarial patient and cadaveric graft survival rates of 98% and 78% respectively at three years post transplant have been reported. Successful transplantation is not only cost effective but the prospects for rehabilitation as measured by school attendance or full time employment are excellent and much better than on dialysis. Unfortunately successful transplantation cannot reverse retarded growth.

There is less experience with liver transplantation but again survival rates continue to improve with a 69% two year patient survival in those less than 15 years of age as reported by the European Transplant Registry. Again the potential for full rehabilitation is considerable and of course there is no other long term support analagous to dialysis in renal failure. Long term follow up after heart and heart lung transplantation in children is limited at present but experience and expertise are increasing and the chances of survival are improving. Corneal transplantation is very successful.

Although it is technically possible to transplant an adult kidney into a child over 2 years of age, an appropriate childhood donor is preferable and this is essential for liver and cardiac transplantation because of the size of these organs.

## The obligation of a children's department

Most paediatricians faced with a child in chronic renal failure would refer him or her to a specialist renal unit and they and the parents would expect him to undergo dialysis until a suitable kidney became available for transplantation. Many paediatricians would feel similarly about a young child with chronic liver disease or an adolescent with inoperable congenital heart disease. Current demands for organ transplantation can only be met if donation is considered in every brain dead child who is being ventilated in an intensive care unit. Doctors who are responsible for the care of such children in one of the country's 22 children's intensive care units or in an adult intensive care unit therefore have an obligation to consider organ donation in every case. It is hypocritical to refer children for a transplant but to approach organ donation in a half hearted way.

## Which children are suitable donors?

Suitable donors are children who are brain dead, ventilated, and with a stable circulation. Clearly the organs to be donated must be functioning well and therefore particular types of injury or illness may make a child unsuitable as a donor. Major head injury or intracranial illness with relative sparing of the other organs are the commonest situations where organ donation is likely to succeed, but donation is possible if there has been sepsis (for example, meningitis and septicaemia) as long as a period of time has elapsed and the sepsis is clearly controlled. Widespread asphyxial damage will often make organ donation impossible, but if there is evidence that after the asphyxial injury renal function is recovering, with a good urine output and falling creatinine, the kidneys may well be suitable for donation. Children dying from malignant disease will not usually be receiving ventilator support but it is possible that a child with a brain tumour might receive intensive care for an acute complication, perhaps related to surgery. Such a child, if brain dead, would be a suitable organ donor. A child of ours with Reye's syndrome was turned down as a kidney donor. Our rule is always to discuss the possibility of organ donation with the local transplant team rather than dismissing it. We have set a lower age limit of 9 months on the donor as transplantation with organs from the newborn and young infant is uncommon and usually unsuccessful. This may change.

## Who should approach the parents, and when?

The most senior doctor who is managing the child's illness and impending death is the person in the best position to raise the subject of organ donation. This usually means the consultant (paediatrician, paediatric surgeon, neurosurgeon) or the senior registrar attached to our children's intensive care unit together with the nursing sister caring for the child. In other units it might be a consultant anaesthetist. Our own feeling is that the transplant team should not do the asking as they have such a powerful vested interest in the reply. The subject of donation is probably best raised with the parents once it is clear that catastrophic brain damage has occurred and a decision has been made to carry out tests of brain stem death. Increasingly we are finding that parents ask about organ donation before it is mentioned to them. Consent is more likely to be given if the request is made positively rather than as an apologetic gesture, and doctors who have little enthusiasm for organ transplantation should allow someone else to talk to the parents. In cases where there has been an accident the parents should be told that the coroner will require a postmortem examination whether or not organ donation is undertaken. The parents need to give their written consent for organ donation but this is obtained later.

## When should the transplant team be approached?

Every hospital where intensive care is carried out has a local transplant team, either at the same hospital or at a nearby centre. The transplant team has a coordinator who is responsible for organising the removal of organs from suitable donors and their transport to a unit (or units) where they will be transplanted. The coordinator may be a permanent appointment to the transplant team or the temporary responsibility of a registrar who is aiming for a career in transplant surgery and engaged in research work. The coordination of organ donation and transplant can be complex and time consuming particularly if multiple organ donation is attempted. The transplant coordinator therefore likes to know in advance that organs may be available. We contact him after the subject has been raised with the parents if they seem to be in favour.

## Care of the child before brain death is confirmed

The overriding responsibility of the doctors and nurses on the intensive care unit is to the child and family, not to the transplant team and organ recipients. Medical and nursing staff should not deal with telephone calls from other hospitals asking for details about the potential donor or requesting extra investigations. Such calls and requests should be handled by the transplant coordinator. However, it is important that careful intensive care of the child continues. Brain death, although likely, is not yet confirmed.

Furthermore if the parents have consented to organ donation, they (as well as the transplant team) will expect the organs to be in a condition that will make successful transplantation likely. Adequate ventilation with monitoring of blood gases must continue and is usually easy to achieve. Infection should be controlled with a broad spectrum antibiotic. Maintaining an adequate blood pressure and effective peripheral perfusion is often difficult in the child with brain stem death because of loss of vascular tone. It is often necessary to give bolus infusions of plasma or saline followed by a maintenance fluid intake that is two to three times greater than normal, and potassium supplements are usually needed. The passage of large quantities of dilute urine is the result of acute diabetes insipidus that follows brain stem death. It will respond to intravenous injections of the vasopressin analogue deamino-D-arginine vasopressin. Occasionally an infusion of an inotropic agent may be necessary.

In our children's intensive care unit this continuing intensive care is carried out by the paediatric medical and nursing staff but some, particularly junior medical staff, may find it unpleasant and distasteful. Those who find it difficult or impossible to give intensive care to a child they know is going to die should not be encouraged to do so.

## Support of the family and staff

The hospital chaplains and children's social workers are experts at listening, supporting, and counselling. They play an important part in helping parents through the period of their child's dying and in bereavement counselling afterwards. They also provide invaluable support to the nurses and doctors caring for the child, both at the time and later.

## Diagnosis of brain death

We use the clinical criteria for the diagnosis of brain stem death that were drawn up by the Conference of Medical Royal Colleges and Faculties of the United Kingdom.[1-3] These are included in a Code of Practice on Cadaveric Organs for Transplantation issued by the Health Departments of Great Britain and Northern Ireland (1983)[4]; the reasoning behind these criteria is powerfully argued by Pallis.[5] There is no evidence to suggest that brain stem death in infants and children (excluding neonates) is somehow different from adults and the same criteria apply. The tests should not be carried out too soon after the original insult (injury, asphyxia, etc), and the younger the child, the longer the time that should elapse before the tests are applied, on the grounds that infants are more resistant to brain insults than older children (although there is little evidence to support this). A period of time allows the parents to see that the diagnosis of brain death is made carefully and without hurry, allows them a little time to make the transition from having a healthy child to the child's death, and allows the medical staff to see whether organs considered for donation are functioning. The pace of events must not be influenced by the transplant team.

The tests are performed by two senior doctors: the consultant responsible for the child's care (or his nominated deputy) and another consultant who is unconnected with either the child or the transplant team. The method of performance of each test is clearly described on a form that is inserted in the child's notes and each doctor has to record each test as it is performed. If the exclusion criteria apply (hypothermia, drug induced coma, use of neuromuscular blockers, metabolic disturbances) the tests are postponed. The tests are carried out on two occasions up to 24 hours apart, depending on the time which has passed since the original insult. The parents must know exactly when each doctor is coming to carry out the tests and their performance takes precedence over other duties.

## After confirmation of brain death

When the second set of tests have confirmed brain death, the parents are told and written consent is given for organ donation. The parents and family must have an uninterrupted, unhurried opportunity to say goodbye to their child in their own time and way. They will then leave the intensive care unit but some will wish to see the body after the organs have been removed, either back on the unit, in the mortuary, or later at the undertakers. It is extremely difficult for parents to leave a child who may simply look to be asleep, and this is a moment that the nursing staff find particularly upsetting.

## Organ removal

The transplant coordinator now takes over all arrangements, fixing up theatres, anaesthetists, blood, transport, etc. He or she may work from a nearby office with a telephone but will not deal with inquiries on the intensive care unit. It may take some hours to make the arrangements if multiple organ donation is being planned but the delay should never be more than 24 hours from the last brain death test and is usually a lot less. The ventilated, brain dead child remains on the intensive care unit receiving the same medical and nursing intensive care from the same staff. They are better able to maintain the organs in optimal condition for removal than the transplant team.

### Certification of death

The child was pronounced dead when the second set of tests confirmed brain death and therefore this date and time should appear on the death certificate.

### Consent for a postmortem examination

This has to be obtained separately from consent for organ donation, although it is not required if the coroner requests a postmortem examination. If a postmortem examination is going to be carried out the pathologist should be approached before any organs are removed so that important evidence of a cause of death is not removed at the same time.

### Notification of the coroner

Organ donation is not an indication for referring a child's death to the coroner, only the cause or circumstances of the death. If the death is due to trauma, follows surgery, or has occurred under suspicious circumstances, the transplant coordinator would ask the coroner's permission for the removal of organs. Sometimes permission will not be given.

### Follow up information

The transplant coordinator will let the staff on the intensive care unit know whether transplant operations took place after organ donation and whether they appear to have been successful. This information is usually given to the donor's parents when they are seen some weeks later for bereavement counselling. It is not appropriate though to give them regular progress reports or to let them know the names and addresses of the recipients, although in some cases this is obvious from reporting in the local or national press.

## Discussion

Since we drew up these guidelines we have had the opportunity to put them into practice on about 10 occasions. There is now a positive attitude towards organ donation on the children's intensive care unit. The number of organs donated has increased and most have been successfully transplanted. Nurses and doctors are able to take pride in the fact that they have given every possible care to the child, have managed the parents throughout the child's illness and death, and have helped other children by ensuring that the donated organs were in the best condition for transplantation. Recognition of this and a word of praise from the transplant team is always welcome.

What of the parents? On media discussions about transplantation, parents of children who have died are sometimes heard to say that they wished they had been asked about organ donation. Others say they are glad they had the opportunity to let their child donate organs so that other children might benefit, thus allowing some good to come from their own tragedy. It would be encouraging if this were so but the benefit to parents of organ donation is perhaps too easily emphasised. There is little information about the impact of organ donation on the subsequent process of bereavement in parents and it is not self evident that it has a beneficial effect. This is an area where research is needed.

The authors are grateful to Sister Pippa Waddington and the staff of the children's intensive care unit at University Hospital for their work, support, and professionalism.

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## *Current topic*

# Fifty years of enuretic alarms

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Enuresis may be defined as an involuntary discharge of urine by day or night, or by both, in the absence of congenital or acquired defects of the central nervous system or urinary tract in a child aged 5 or over. Oppel *et al* in their study of 859 children showed that 10% were wetting at age 7 and the National Child Development Study of all children born in England during a week in 1958 showed on follow up that approximately 12·5% were wetting at 5 and 10% at 7 years.[1 2]

Ackerson in 1931 stated that despite unremitting efforts to develop a specific form of treatment nocturnal enuresis continued to be regarded as an unsolved problem.[3] In 1950 Crosby commented that medical practitioners had been so discouraged over the results of treatment in the past that there was a widespread tendency to counsel parents 'to wait and let the child grow out of it'.[4]

By 1958 Wickes was able to find only one report detailing the use of an alarm in the United Kingdom and in 1960 Eysenck claimed that not a single child guidance clinic in the British Isles employed the conditioning treatment for enuresis.[5 6] In Canada only 10% of paediatricians at the Montreal Children's Hospital approved of an alarm bell.[6] The eminent adult neurologist Walshe in a letter to the *Lancet* in 1964 was scathing in his criticism of the use of this 'barbarous contraption'.[7] Several psychiatrists were of the same opinion and were probably responsible for curtailing its use and development. Werry wrote in 1966 'Although references to conditioning treatment will be found in most orthodox pediatric texts, the method has never really become popular at least in medical circles and is at best regarded as a last-ditch treatment'.[8] Twenty years later, according to Foxman *et al*, enuresis alarms continued to be recommended by only 3% of American paediatricians.[9]

It seems appropriate, as the 50th anniversary of Mowrer and Mowrer's excellent paper was celebrated recently,[10] that the most successful treatment of nocturnal enuresis to date—that is, the conditioning method—should be reviewed. In 1938, Mowrer and Mowrer argued that 'if some arrangement could be provided so that the sleeping child would be awakened *just after the onset of urination,* and only at that time, the resulting association of bladder distension and response of awakening and inhibiting further urination should provide precisely the form of training which would seem to be most specifically appropriate'.[10] To this end they designed a pad of bronze screening and absorbent cotton fabric which when wet with urine, activated an electric door bell to waken the child.

Mowrer and Mowrer used this apparatus for three years before publishing their results, at first believing they had pioneered alarm treatment.[10] In 1936, however, Svordlovsk, a Russian scientist, announced his gift to Soviet motherhood—'a light which flashes when the baby needs changing. Wires attached to strips of tinfoil in a special packet with cloth sandwiched between, becoming a conductor when dampened and presto a light goes on'.[11] Seiger patented a similar apparatus in the United States in 1936.[12] A more detailed search of the literature showed that Pfaundler, a German paediatrician, had developed equipment in 1902 to signal by a bell that an infant needed changing.[13] He tried it on an enuretic child for a month with appreciable reduction of wet beds, and stated that, in some cases, the knowledge that urination at night would cause the bell to ring henceforth inhibited this act. Genouville and Remy-Roux both used Pfaundler's method and reported good results.[14 15] Genouville found the sound of the bell almost always inhibited further urination even though it did not at first produce wakening.[14] Although Genouville and Remy-Roux claimed considerable success for their treatment, it failed to be taken up, largely because of the cumbersome nature of the equipment and the fact that a considerable amount of urine (20–30 ml) was necessary to activate the electrodes.[14 15]

## Mode of action

The fundamental principle of the alarm is to change the meaning of full bladder sensations from a signal to urinate to a signal to inhibit urination and waken. Mowrer and Mowrer used a classical conditioning paradigm to explain the action of the alarm. They proposed that sphincter contraction and wakening becomes a conditioned response to bladder distension by association in time with the alarm.[10] This model has been questioned because of the expectation that extinction should occur with the removal of the alarm.

Lovibond viewed the alarm as an aversive stimulus which the child learns to avoid by sphincter contraction and wakening, and thus explained the mode of action as conditioned avoidance.[16] Increased functional bladder capacity has been claimed to occur with alarm treatment,[17] and this may be a consequence of holding.

The typical consequences of a wet bed are what Azrin *et al* call motivational and social variables.[18] They proposed that as wakening to the alarm ensures the consequences occur close to the time of the accident, learning of bladder control is based on operant principles.

## Three types of alarm systems

There are basically three types of alarm systems:

### (1) THE PAD AND BELL

This was used by Pfaundler, Genouville, Remy-Roux, and Svordlovsk and originally consisted of zinc-copper plated iron ore wire nets, 10″ square.[11 13–15] The pads were separated by a linen or cotton sheet. In 1938 Mowrer and Mowrer increased the size of the pads to 28″ by 32″.[10] Seiger invented and patented a single pad of rubber 8″ by 10″ with an inlay of parallel wires made of a nickel chrome alloy.[12] This pad was easier to clean and dry and was activated by a smaller amount of urine. However, the pad was small therefore, not surprisingly, when the apparatus was sent to the Quarrier Homes in Scotland in 1949, the size of the rubber pad was increased to 18″ by 24″ and the nickel wires were arranged in a circular manner ½″ apart.[19]

Gillison and Skinner showed that it required 5 ml of urine to activate this type of alarm.[20] Wickes introduced gauze pads and later aluminium foil pads were used by McKendry *et al.*[5 21] The original upper aluminum pad had ¾″ perforations, but because of the occurrence of ulcers the perforations were reduced to ½″ in diameter and set 1¼″ apart.

Presently the types of detector mats used are (a) a single PVC sheet with stitched circuit or printed circuit, (b) a pair of wire mesh mats, and (c) a pair of conducting sheets, the top perforated with ¼″ holes. Goel *et al* comment that no mats were entirely satisfactory, although clinical personnel preferred the wire mesh type.[22]

### (2) THE BODY SENSOR PLUS ALARM

This was pioneered by Crosby.[4] For males the sensor was held by a plastic tube attached to the penis and for females the sensor was contained in a sanitary like pad. When the electrodes were activated a light went on at the bedside, the alarm rang and a mild shock was delivered to the loin or lateral abdominal wall. A similar apparatus was used by McKendry *et al.*[23]

### (3) THE BODY WORN ALARM

According to Schmitt this has ‘revolutionised’ the treatment of bedwetting.[24] There are basically two formats: (a) two electrodes or sensors attached to the child's underwear by two clips and the buzzer is worn on the wrist and (b) a sensor on a small plastic card that is inserted into a pocket inside the underwear and the buzzer is attached to the pyjama jacket.

## Cost

The pad and bell apparatus range in price from £17 to £52 with a mean of £31.[22] They are supplied with pads, which may require replacing regularly, and a new set is certainly recommended for each patient. A pair of pads may cost up to £7 and thus greatly increases the running cost of the pad and bell.

British versions of the body worn alarm currently cost from £27 (Night Trainer supplied by Nottingham Rehab) to £32 (Mini Dri-Nite supplied by Eastleigh Enuresis Alarms). American versions cost £25, which according to Moffatt *et al* is approximately half the price of the pad and bell apparatus available in the United States.[25]

## Age to begin treatment

Mowrer and Mowrer stated that treatment with the alarm should not be started before 3 years of age.[10] Crosby in his study of 52 children treated five aged 3 to 4 years and Gillison and Skinner treated 19 children between 3½ and 4 years claiming a 74% success rate.[4 20] Young and Morgan maintained that urinary continence is achieved at 3 but did not start treatment until 4 years of age.[26] Forsythe and Redmond used the alarm on selected children at 5, while Meadows recommended its use at 7, and Schmitt at 8 years of age.[27–29] As regards the body worn alarm Schmitt recommended using from the age of 7.[29]

## Advice to parent and child

Before supplying any enuresis alarm it is essential to obtain an accurate history of sleeping arrangements and toilet facilities. It is imperative to decide who will be responsible for supervising the child when the alarm rings, who will dry and replace the pads, and who will keep the record card (preferably the child supervised by a parent). The apparatus must be demonstrated in the clinic and with the pad and bell the importance of the quality of the separating sheet and placement of the clips must be emphasised. Wire foil pads must be checked daily and replaced if frayed. The parent should be shown how to check the battery. Contact with the therapist once a fortnight during the 16 week treatment period is recommended by Meadows.[28]

Mowrer and Mowrer emphasised the discontinuation of lifting, no fluid restriction, of sleeping nude below the waist, encouraging the child to go to the toilet when the alarm rings, and if not wakened by the bell a parent must waken the child.[10] They also advised practising going to the toilet if the child wakened spontaneously, all of which continues to be good advice today. Detailed procedures for using the pad and bell are outlined in papers by Dische and Butler.[30 31]

## Hazards of enuresis alarms

In 1958 Gillison and Skinner, using a Quarrier type of pad, reported that 23% of their patients developed a rash on the buttock or thigh.[20] They discovered if the bell rang within seconds there was no problem, but if the bell failed to ring a papular rash could occur and in more severe cases punched out superficial ulcers. They recommended covering the upper pad with a double drawsheet and dusting the skin with boric acid powder. Borrie and Fenton reported two children using the same type of pad who developed painless ulcers within 24 hours.[32] They showed ulcers could occur if the battery was faulty or run down, the alarm was not activated, if the patient failed to waken, or if the amount of urine was too small. It was reported that ulcers occurred on all parts of the body in contact with the pad—for example, arm, costal margin, lumbar area, buttocks, etc. Greaves described similar ulceration when aluminium foil pads were used especially when the upper pad had large perforations.[33] Reduction in the size of the perforations to ½″ in size and set 1¼″ apart lowered the incidence of ulceration, but it did not disappear. Coote showed that perspiration and a pad that crumpled, not urine, could cause weals and ulcers.[34] In order to overcome this problem Coote produced a stiff pad with recessed electrodes.[34]

From the above experience it has been recommended that (a) the battery should not be allowed to rundown, (b) the child must be awakened when the alarm rings, and (c) the child should not be able to disconnect the alarm system.

## Survey of reported studies

After Mowrer and Mowrer's paper there have been many reports of the enuresis alarm.[10] There is, however, enormous variation in the type of information especially with regard to criteria of arrest and relapse, methods of measuring effectiveness, and adjuncts to alarm treatment. This makes comparison of studies difficult.

Standardisation of criteria is important if progress in our understanding of alarm treatment is to continue. Table 1 shows 34 studies where criteria of initial arrest was stated and subjects numbered 15 or more. A review of the studies suggest important factors in reporting results appear to be:

### (1) SEVERITY

Dische *et al* stated that the lack of a standard baseline period for the collection of data before treatment is common to many studies.[35] They used a nine week baseline while others such as Sacks and DeLeon and Fielding used a four week baseline.[36 37]

In the literature the degree of severity before alarm treatment has inevitably varied. The criteria of wet nights/week for inclusion in a study have ranged from seven nights a week to one night a week.[37 38] As table 1 shows only 12 (36%) studies reported criteria of severity.

### (2) ASSOCIATED DIURNAL ENURESIS

Fielding found the enuresis alarm was much less effective with children suffering from both nocturnal and diurnal enuresis when compared with a group of children with nocturnal enuresis.[37] Thus studies including children with nocturnal and diurnal enuresis might be expected to be less effective. Only eight (24%) of the reviewed studies reported whether such children were included in the sample.

### (3) PREVIOUS ALARM TREATMENT

Fielding discovered that children who had previously been unsuccessfully treated with the alarm were less likely to succeed with a further course of treatment than previously untreated children.[39] Only six (18%) of the reviewed studies made reference to whether children had been treated previously with the alarm; three studies included such children and three studies excluded such children.

### (4) DURATION OF TREATMENT

In Doley's survey of the pad and bell, treatment

Table 1 *Studies of initial arrest, drop out, and relapse in the three types of enuresis alarm*

| | *Year* | *No of children* | *Age range (years)* | *No of wet nights/week* | *Criterion for initial arrest (No of dry nights)* | *No (%) with initial arrest* | *No (%) who dropped out* | *No (%) who failed* |
|---|---|---|---|---|---|---|---|---|
| **Pad and bell** | | | | | | | | |
| Mowrer and Mowrer[10] | 1938 | 30 | 3–13 | – | 7 | 30 (100) | – | 0 |
| Baller and Schalock[52] | 1952 | 52 | 5–17 | – | 10 | 51 (98) | – | – |
| Behrle *et al*[53] | 1956 | 20 | 5–14 | 4–7 | 7 | 19 (95) | 2 (10) | 4 (20) |
| Freyman[54] | 1963 | 50 | 5–15 | – | 14 | 34 (68) | – | 20 (40) |
| Taylor[55] | 1963 | 94 | 5–15 | – | 21 | 64 (67) | – | 19 (21) |
| Werry and Cohrrsen[56] | 1965 | 22 | – | – | 28 | 13 (59) | 4 (18) | – |
| Young and Turner[57] | 1965 | 105 | 4–15 | 3–7 | 14 | 69 (65) | – | – |
| DeLeon and Mandell[50] | 1966 | 56 | 6–13 | – | 13 | 44 (81) | 3 (15) | – |
| Novick[58] | 1966 | 36 | 6–13 | – | 14 | 32 (89) | – | – |
| McConaghy[59] | 1969 | 20 | 4–15 | – | 14 | 14 (70) | 3 (15) | – |
| Forsythe and Redmond[27] | 1970 | 200 | 5–15 | 6–7 | 28 | 132 (66) | – | 49 (18) |
| Turner *et al* [60] | 1970 | 15 | 4–15 | 3–7 | 14 | 12 (80) | – | – |
| Dische[30] | 1971 | 84 | 4–15 | 3–7 | 21 | 70 (83) | – | 12 (14) |
| Young and Morgan[48] | 1972 | 144 | 4–15 | – | 14 | 101 (70) | 43 (29) | – |
| Collins[61] | 1973 | 20 | 4–12 | – | 10 | 13 (65) | – | – |
| Taylor and Turner[62] | 1975 | 21 | 4–16 | 1–7 | 27/28 | 13 (62) | – | – |
| Sacks and DeLeon[36] | 1978 | 30 | 5–14 | – | 13 | 18 (66) | 5 (16) | – |
| Fielding[37] | 1980 | 75 | 5–15 | 4–7 | 14 | 35 (47) | 23 (30) | – |
| Bollard and Nettelbeck[63] | 1981 | 20 | 5–14 | – | 14 | 16 (80) | – | – |
| Berg *et al* [64] | 1982 | 54 | 5–14 | – | 24/28 | 34 (63) | 14 (26) | – |
| Dische *et al* [35] | 1983 | 126 | 4–13 | – | 21 | 95 (75) | 13 (10) | – |
| Sacks and DeLeon[65] | 1983 | 65 | 5–15 | – | 13 | 44 (70) | 11 (17) | – |
| Goel *et al* [22] | 1984 | 100 | 7–14 | – | 24/28 | 45 (45) | – | – |
| Netley *et al* [66] | 1984 | 31 | 6–12 | – | 56 | 19 (61) | – | – |
| Butler *et al* [45] | 1988 | 28 | 6–14 | 4–7 | 14 | 14 (70) | 8 (29) | – |
| Fordham and Meadow[47] | 1989 | 27 | 6–16 | 2–7 | 42 | 4 (15) | 10 (37) | – |
| Total | | | 1525 | | | 1035 (68) | | |
| **Body alarm plus sensors** | | | | | | | | |
| Crosby[4] | 1950 | 45 | 3–14 | – | 14 | 43 (95) | 2 (4) | 2 (4) |
| McKendry *et al*[23] | 1972 | 137 | 5–20 | – | 26/28 | 113 (83) | 4 (3) | 18 (13) |
| Total | | 182 | | | | 156 (86) | | |
| **Body worn alarm** | | | | | | | | |
| Arroe and Rasmussen[67] | 1979 | 59 | 6–15 | 5–7 | 14 | 40 (68) | – | 17 (30) |
| Shapiro[68] | 1985 | 200 | 6–16 | – | 21 | 140 (70) | – | 30 (15) |
| Moffatt *et al* [25] | 1987 | 66 | 8–14 | – | 14 | 42 (69) | – | 8 (13) |
| Dunn* | Unpublished | 125 | 5–12 | 3–7 | 27/28 | 95 (76) | – | 26 (20) |
| Butler *et al* [41] | 1989 | 44 | 6–15 | 4–7 | 14 | 34 (77) | 3 (7) | 7 (16) |
| Fordham and Meadow[47] | 1989 | 29 | 6–16 | 2–7 | 42 | 6 (21) | 11 (38) | |
| Total | | 523 | | | | 357 (68) | | 88 (18) |

*Dunn BL. Treatment of enuresis with a portable alarm—a study of 125 children (personal communication).

ranged from five to 12 weeks, while Schmitt's review of American versions of the body worn alarm suggested eight to 12 weeks.[40 29] Butler and Forsythe found with the British version of the body alarm that 71% of children achieved dryness within eight weeks.[41]

A time limit is important as the longer a child uses an alarm, the less certain we can be that a successful result is due to this treatment because of the spontaneous remission rate.[27] Recent studies have accepted 12 to 16 weeks as the treatment duration, children not reaching the initial arrest criteria during this period being considered failures.

### (5) DROP OUT

Johnson makes the point that given the effort and patience required to use the alarm efficiently some drop outs would be expected.[42] Drop out has tended to include: (a) patients failing to attend the clinic and (b) patients stopping treatment before a reasonable time has elapsed.

In practice and in the review of studies it has proved difficult to separate the reasons for drop out. Maternal intolerance has been found to be predictive of drop out.[43–45] A problem, highlighted by Johnson in comparing studies, arises where effectiveness is reported after excluding drop outs.[42]

The more accurate results are those that quote success as a percentage of the total sample.

(6) EFFECTIVENESS

Early studies of alarm treatment seldom used criteria to discriminate between success and failure, but utilised terms such as 'improved', 'completely dry', and 'temporarily favourable'. Later studies relied on vague or questionable definition—for example, 'stopped altogether or having occasional accidents',[23] 'less than 4 wet in 28 days before treatment stopped'.[22]

Dische *et al* used the term 'initial arrest' to distinguish those children responding initially to the alarm from those failing to respond: this was the time when the alarm was removed.[35] This criteria of initial arrest is based on the achievement of an arbitrary number of consecutive dry nights, which has ranged from seven to 42 nights.[46]

Table 1 shows 16 (49%) of the studies used 13 to 14 consecutive dry nights as an initial arrest, and this might therefore be taken to indicate the criteria to use in the future. It has been suggested the longer the alarm is continued after the child becomes dry the less likelihood of relapse.[27] However, one of us (WIF) has re-examined the record cards of the 200 children included in a previous study plus an additional 75 consecutive children, which has shown that of those children who achieved a week's dryness 44% would have relapsed, two weeks' dryness 18%, three weeks' dryness 16%, and four weeks' dryness 15%.[27] It would appear therefore that no significant benefit is obtained by continuing the alarm for more than two weeks after the child becomes dry. Using the author's own criteria of initial arrest, with the pad and bell in 26 studies there was 68% initial arrest with 1525 children, while with the body alarm plus sensor there was 86% initial arrest in 182 children (two studies) and with the body worn alarm in six studies there was 68% initial arrest with 523 children (see table 1). Thus there appears little to choose between the two commonly used methods in terms of initial effectiveness. A recent comparison of the body worn alarm plus pad and bell by Forham and Meadow confirms this finding, although with an 'unusually stringent' criteria of initial arrest few children in either treatment overcame bedwetting.[47] Butler *et al* in a comparison of the two types of alarm showed little difference in terms of effectiveness, but the body worn alarm was superior in terms of speed of acquisition of dryness.[41]

(7) FAILURE

In their study of 30 children, Mowrer and Mowrer stated that all became dry in eight weeks and relapses were rare.[10] Failures did not appear to occur, which is unusual. A 100% success did not appear in the literature when drop out from treatment and a specified treatment duration were reported.

There are reported failure rates (in 10 studies) with the pad and bell of 17% (range 14–40%), for the body sensor plus alarm (in two studies) of 11% (range 4–13%), and in body worn alarm (in five studies) of 18% (range 13–30%). Again there appears little to choose between the pad and bell or body worn alarm in terms of failure. There are many explanations for failure such as lack of parental supervision, failure to waken, lack of toilet facilities, two sharing a bed, domestic problems, refusal to use the apparatus, inadequate instruction, faulty equipment, the child's lack of interest, to name but a few. Work by Dische *et al* indicates lack of response may be predicted where there are family difficulties and unsatisfactory housing.[35] Even if these factors are considered, however, there is a group of children (approximately 10–15%) who use the pad and bell correctly and do not become dry.

(8) RELAPSE

A review of the literature shows little agreement as to what constitutes a relapse. It is therefore not surprising that a comparison between reported relapse with pad and bell and body worn alarm treatment is difficult. Since 1980 studies have reported between 29%, within six months,[48] and 66% within 12 months[37 49] of children returning to bed wetting after initial arrest.

Most relapses are likely to occur in the first six months after initial arrest.[35 40] In order to avoid further confusion one option would be to document the number of bed wetting accidents in the six months following treatment. Thus *continued arrest or six months arrest* would be defined as *no wet nights during the six month follow up*. Adopting such a criteria DeLeon and Mandell found only 20% of children remained free of accidents.[50]

In order to test the feasibility of this definition the record cards of 275 children treated by one of us using a pad and bell alarm with two wire mesh mats were reanalysed.[27] Table 2 shows the results and suggests if those relapsing and treated a second time are included, 160 (58%) children had a 'continued arrest' for six months.

It has not been possible to extract similar information from any of the published reports. Although accepting six months as a 'vulnerable' period for relapse, a two year follow up is essential before relapse can be excluded. For example, Forsythe and Redmond found 10 relapses occurred between seven

Table 2 *Summary of 275 children with nocturnal enuresis treated with a pad and bell*

| | *No of patients* | *No (%) dry* |
|---|---|---|
| Initial arrest (28 nights) | 275 | 166 (60·4) |
| Continued arrest (six months) | 275 | 136 (49·5) |
| Relapsed within six months | 166 | 30 (18·1) |
| Initial arrest with second course of treatment | 30 | 24 (80·0) |
| Continued arrest with second course of treatment | 30 | 24 (80·0) |
| Continued arrest with one or two courses of treatment | 275 | 160 (58·2) |

and 22 months and Bostock, using the 'Crosby' body worn alarm, reported a child who relapsed 30 months after withdrawal of the alarm.[27 51] A two year *accident free period* has been termed by Dische *et al* as *'complete arrest'*.[35]

Many parents fail to reattend after a relapse because of uncertainly about the alarm's effectiveness a second time. Approximately 60–82% of children, however, achieve 'continued arrest' with a second course of treatment with the pad and bell. There is no similar information on the body worn alarm. Thus in reporting the results of alarm treatment it is suggested the following information is important:

- Severity—frequency and duration of wet beds before treatment and the criteria of wet nights/week for inclusion in the study.
- Associated diurnal enuresis—percentage of such children included.
- Previous alarm treatment—percentage of such children included.
- Duration of treatment.
- Drop outs from treatment.
- Degree of supervision during treatment.
- Initial arrest criteria.
- Failures to meet the initial arrest criteria.
- Relapse—measured by a criteria of 'continued arrest' (six months) and 'complete arrest' (two years).

## Consumer appeal

Fordham and Meadow found advantages of the body worn alarm over the pad and bell were the small size, rare false alarms, comfort, sensitivity to urination, and cheaper price. The disadvantages of the body worn alarm (Mini Dri-Nite) such as fastenings, detachable leads, and sensor falling out of the pant liner are overcome by the design of the Night Trainer. In the study of Butler *et al,* 24 children had experience of both the pad and bell and body worn alarm, so were able to make a comparison between both types.[41] Only one child expressed a preference for the pad and bell over the body worn alarm because she slept nude and had nowhere to pin the alarm (a wrist alarm would have overcome this difficulty). Some boys expressed concern at having to wear an absorbent pad, but none refused treatment. Most preferred the body worn alarm because: (1) the small size of the apparatus made it less conspicuous and was more portable going to stay with a friend or on holidays. (2) The child was more involved with all aspects of the procedure. (3) It was more effective waking the child than the pad and bell apparatus. (4) It was more comfortable than lying on gauze mats, etc. (5) It was activated by a smaller amount of urine and on many occasions the bed sheets remained dry.

Although therefore the pad plus bell and body worn alarm appear comparable in terms of initial arrest and failure rates, what evidence there is suggests the body alarm is preferred by those it is designed to help—the children.

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*Archives of Disease in Childhood,* 1989, **64,** 886–888

## *Personal paper*

# The other end of the telephone

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The General Medical Council advocates a broad experience in general professional training for doctors intending to be specialists and has indicated that a period in general practice would be beneficial. Trainee posts are usually available only to those planning a career in general practice. The Education Committee for General Practice, of the University of Newcastle upon Tyne, however, has recently made available a small number of trainee posts for doctors planning to remain in the hospital service. I was fortunate to spend six months of my two year paediatric rotation in general practice in the Northumberland market town of Hexham.

When the suggestion was first made that I should apply for such a post, I treated it with a great deal of caution. I feared members of a future interviewing panel would shake their heads over my curriculum vitae and ask me searching questions about why I had taken my foot off the ladder of career paediatrics. The panel was sure to follow the conventional view at my medical school that it was unhelpful, even detrimental, to supplement hospital training with experience in general practice. My exposure to three aspects of practice convinced me that this view was misguided. These were the decision of referral, the management of trivial problems, and the development of a rapport with my patients.

## Referral

In an average week each partner in my practice would refer seven non-acute and two acute patients for care by other doctors. There was, therefore, no shortage of opportunity to sharpen my skills at this form of decision making, a process which was hardly mentioned at my medical school, and which in hospital practice was too often left to the last minute as a sign of clinical ignorance or defeat.

The most stressful of these decisions was the referral of an acute admission. My previous involvement had been as the duty houseman on the other end of the telephone, woken at 3am from much desired sleep, when I considered a request for admission from a general practitioner to be both a 'fait accompli' and a prime example of 'passing the buck'.

The telephone call, I now realise, hides too well the minutes or hours of painful indecision that may have preceded it. It is not easy to weigh up the pros and cons such as degree and severity of illness or amount of family support, which are not measurable in simple units. For example, to what extent should the distance to the referral centre (22 miles for paediatric cases) influence whether illness of a certain severity be cared for at home? Or, how much should assessment of the patient's insight into the nature and dangers of the illness influence me in postponing an admission? Alarmingly, I found that my equation involved some unwelcome and more subjective variables like intellectual curiosity, professional pride, how many patients there were still to see and, of course, fatigue.

I did not solve all the problems involved in referral, although I found that a scrap of paper listing items that I and the hospital could and could not offer, made difficult decisions easier. If this failed, discussion with the hospital doctor often helped. In any event, upon my return to hospital I would certainly never ask the general practitioner the patient's hospital number or rectal temperature as the poor man may be standing in the one and only windswept coinbox on a council estate clutching his last 10 pence piece, and fighting off a stray Alsatian.

## The problem of trivia

I saw about 120 patients each week in a surgery that was open to any of the 8000 residents on the practice list, and it was not surprising that much of the work involved seemingly trivial problems. At medical school the emphasis had been on the management of diseases with dynamic pathology, and patients that presented in hospital with minor illness were often discharged to the care of their general practitioner. I, therefore, felt inadequately prepared for this type of work. Special problems arose from the twin enemies of boredom and helplessness.

My initial boredom arose from a perceived lack of challenge in diagnosis and management. This soon changed. I discovered that trivial problems for the doctor did not necessarily seem so to the patient. My intellectual pride had let me believe that a patient with an 'interesting' disease, such as carcinoid syndrome, should feel worse than one with a 'trivial' disease, such as a cold. It did not take many surgeries to learn how rotten and depressed tonsillitis or otitis externa can make someone feel. Not only did many of my patients with 'trivial' disease feel awful, but they also thought they had something very serious. It was a source of quiet satisfaction to reassure all these unhappy people. Two patients thought that their viral upper respiratory infections were in fact AIDS and leukaemia and were very relieved by our discussion.

Another challenge was to maintain my sharpness for diagnosis, surgery after surgery, spot after spot, cough after cough. I tried to develop a set of clinical alarm bells that would ring even if coffee was only 10 minutes away. Of course, we all use these in hospital medicine but I never found them more helpful than in practice. The bells often coaxed me into action in the warm surgery where a soporific mood was so easily encouraged by the plush leather upholstery and homely matching of carpets, curtains, and wallpaper.

Another helpful approach was to ask about each patient, 'Why has he come to see me?' Failure to ask this allowed me to miss recognising a prolonged grief reaction presenting as persistent frontal headaches.

I experienced helplessness frequently when dealing with the commoner complaints of practice because I felt I had insufficient to offer by way of explanation or treatment. Too often I tried to hide this by replying in a stereotyped manner:

'Oh yes, very red, Mr. N...... likely to be a virus though, very common in Hexham at this time of year ........ no point in antibiotics, it doesn't look that sort ........'.

Curiously, I did find that most of Hexham still recognises the word 'virus' as a code for something harmless despite the advent of AIDS and oncogenes. But they also recognised my lack of sincerity and many of these patients turned to my trainer for a more satisfying response. A kind and honest explanation of my ignorance about even common diseases was, I soon discovered, the route to success.

Many of the common illnesses of practices naturally are paediatric and I had the opportunity of seeing many conditions that rarely if ever reach hospital. These included my first sighting of measles in two years of paediatrics, chilblains, glandular fever, and hand, foot, and mouth disease. Seeing so many cases of diseases such as rubella and glue ear gave me a clear picture of the range of severity, the various forms of presentation, and the vast potential for epidemiological research in practice.

## Getting to know the patients

Furthering my insight into the intimate lives and background of some of my patients was a rewarding part of my attachment. What I managed to learn in six months was small in comparison with the knowledge of any of the partners who had each worked at the surgery for between 18 and 25 years. I should be surprised if anyone in the town, except perhaps the receptionists, held their ears to the ground quite so closely as did my trainers! Any paediatrician will forget this at his peril. If one needs to know more of Hexham's complicated genealogy, which children are most endangered by abuse or even who beats their wife and how often, one need go no further than my trainers.

To my surprise I did get to know some families very well in six months. One such family lived in the poorer east end of Hexham. On only my second day in surgery Mrs J brought her 3 year old daughter, Emma, along complaining that the girl had developed puffy eyes over the previous week. Despite exhortations on the vocational training course that general practice was not about discovering clinical 'gems' to be passed on to the master jeweller in the city, I found her to have gross proteinuria and dutifully sent her to hospital with a provisional, and soon substantiated, diagnosis of nephrotic syndrome. I soon found out that such a case should be diagnosed once in every 20 general practitioner years and so felt naturally very proud that I had unearthed a diamond. Fortunately for myself, I did not spend the remaining six month searching for another, although several others came my way. There were more precious stones to be found in other forms.

After some two weeks in hospital Emma's urine was pronounced clear after a course of steroid treatment and she was released home. As was usual in the practice, I visited the home after discharge and except for Emma's occasional steroid induced extroversion and a sleep reversal pattern, all seemed well in the household.

At this stage I might have understood her medical condition but I turned out to understand very little of what was happening in the family. My next contact with Mrs J and Emma came when they turned up at the surgery clutching a low salt diet sheet and complaining that all the foods turned out to be too dry. Although I did not realise at the time, the long list of the foods that her daughter was forbidden had dulled her mind of ideas for attractive juicy food. Rather misguidedly I thought that my suggestion of low salt white sauce would sort out the problem. This was greeted by Mrs J with a blank stare as she had never made white sauce. Nor could Mrs J's mother, who was summoned from the waiting room to help us out of this impasse. We all eventually settled for a simple gravy from vegetable water, flour, and browning!

Two weeks later, Mrs J returned to my surgery in tears. To my surprise she had left her husband, driven out, she said, by threats of beatings and some Scrooge like financial dealing by her husband, who preferred to drink his earnings rather than feed and clothe his two children. This left Mrs J poorer still, isolated from their shared friends, and very depressed about looking after her children in her mother's small spare room in her council house. Emma's recent illness did not help her peace of mind. As she sat there crying in my surgery I realised how little I knew of her lifestyle and the problems that brought about and had been caused by her separation. Over subsequent weeks Mrs J returned on numerous occasions to my surgery, often with the excuse of a problem with Emma or her brother. These visits allowed me to sketch in some of the background information especially concerning Mrs J's family upbringing and Mr J's drinking habits, which had contributed to the breakup. Getting to know this family so well certainly made me wonder how it was possible to make judgments about the future of problem families with less information. Could an estranged hospital doctor in the unsettling ward atmosphere have hoped to gain a similar degree of insight as I had achieved in my patient's natural home? Such an experience left me in no doubt about the important part that the health visitor and general practitioner play in social paediatrics.

## Coda

I thoroughly enjoyed my six months as a general practitioner trainee. It is a reflection on the limited nature of my medical training that so much of the experience was new. I no longer feel apprehensive about discussing this post in front of my next interview panel. A sceptical member may expect me to justify that most of the time was spent with non-paediatric cases. I would explain that in addition to helping me with the specific areas described above, it has provided inside experience of a system in which most paediatric consultations take place and upon which the smooth running of hospital care depends.

I hope that this explanation will not be necessary when in future it is looked upon as an essential, not additional, preparation for a career in hospital paediatrics.

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*Archives of Disease in Childhood,* 1989, **64,** 889–893

# Correspondence

## Value of ultrasound in differentiating causes of persistent vomiting in infants

Sir,

The practice of neonatal cranial ultrasound was essentially developed by paediatricians. Obstetric ultrasound similarly in its early stages was the preserve of the obstetrician and in many hospitals the responsibility for provision of this service remains shared by clinician and radiologist. Such developments arose mostly from lack of radiological resources and partly admittedly from disinterest of radiologists.

It has become evident recently that some neonatologists, in particular, are using ultrasound for the evaluation of abdominal pathology, for example, in differentiating causes of persistent vomiting in infants. Demarcation disputes can be counter-productive but many radiologists view this change of practice with considerable anxiety and disapproval.

Errors of observation and interpretation will be made by incompletely trained ultrasonologists and these will be compounded by failure to appreciate the particular place of other imaging techniques. Moreover, if hard copies of images are made these become part of the patient's records and as such can constitute with any report thereon tangible evidence should litigation arise. The occasional ultrasonographer would then have to justify his or her competence (or incompetence!).

Ideally, radiological procedures in their broad definition should be left to radiologists. If radiological resources are insufficient, ask for more.

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## Deliberate self poisoning in adolescents

Sir,

The article by Clarke comments upon the difficulties caused by poor compliance in self poisoning adolescents.[1] She also says that an 'appreciable' number of children have unacceptably long hospital stays, but does not define what an appropriate stay should be.

In 1988, six adult women under the age of 30 were referred to me by their general practitioners for counselling. All had long histories of significant psychiatric problems that dated back to childhood and had records of poor school performance and truancy. Three had been admitted to hospital under the age of 15 years with self poisoning. All six disclosed serious childhood sexual abuse. None would contemplate referral to either social services or psychiatry as both agencies had been involved in the past.

What interested me was the clarity of recall of the three who had made suicidal attempts, and the remarkable consistency of their perceptions of these events. 'The psychiatrists seemed more interested in my parents.' 'They just sent me straight back home'. '*He* (the abuser) just sat there all day—it was worse than being at home.' 'They wouldn't have believed me anyway.' 'They told them (parents) that I didn't really mean it.'

Dr Clarke acknowledges that sexual abuse has been underestimated in the statistics. I would suggest that this factor may be of very serious significance in the background of large numbers of self poisoning adolescents and that poor compliance with follow up must be viewed in the context of professional failure to recognise this and act accordingly.

The women who spoke to me perceived the standard psychiatric approach (that is, rapid assessment, early discharge, close involvement of parents) as a betrayal of their interests. Dr Clarke proposes no way by which young victims of chronic sexual abuse can be helped to individuate or feel safe. To blame the victim for poor compliance and simply propose more of the medicine that fails seems to me most unhelpful. One woman I spoke to appeared to be more hostile towards and angry about the psychiatrist than the perpetrator of the abuse.

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## Diagnosis of brain death by transcranial Doppler sonography

Sir,

The paper published from Freiburg by Bode *et al* points to a particular pattern of sonogram which is characteristic of brain death.[1] The sonogram obtained from the basal cerebral arteries shows a major degree of reversed flow in diastole. We agree with the basic conclusion of the paper and having noted this phenomenon over the past three years published the validation of its use in clinical practice in 1987.[2]

We analysed the sonograms from 23 children with very bad outcome out of a total series of 80 children monitored in coma. We thought it important that the sonogram was expressed numerically and therefore transformed the waveforms into a direction of flow index, DFI=1−R/F where DFI is direction of flow index and R and F are reverse and forward flow respectively.

Our conclusions were: (1) that once a middle cerebral artery signal had been observed after a 30 minute period with a time/velocity of less than 10 cm/s and/or a direction of flow index of less than 0·8 recovery of forward flow throughout diastole was never observed and no patient recovered brain stem reflexes. Where flow index was above these limits but with reverse flow in diastole recovery could occasionally be seen. The direction of flow index could occasionally drop below 0·8 briefly but when persisting for 30 minutes yielded no false positive results. (2) For medical and legal purposes we decided that no decision could be taken as a result of the inability to find a middle cerebral artery signal. Our study was not attempting to answer this question in the neonatal period.

Because of the high degree of concern about possible errors in the diagnosis of brain stem death we were permitted by the editors of the *Journal of Neurology, Neurosurgery, and Psychiatry* to publish quite a lot of the clinical and sonogram data in its primary form. By validation of phenomenon we mean that no clinical notice was taken of the sonogram and the children fulfilled the United Kingdom criteria for brain stem death over the appropriate time. We did not persist with intensive care until the heart stopped. At a recent meeting this additional method of confirming brain stem death was accepted by a number of people in the field as reliable outside the newborn period.

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## Hyperventilation in the awake state in children with autistic traits

Sir,

Southall *et al* reported on hyperventilation in association with Rett syndrome.[1] Hyperventilation is a behavioural trait common to Rett syndrome, infantile autism, and autistic traits resulting from severe organic brain damage.[2] We had the chance of studying six children (four girls, two boys) belonging to the last group, who underwent polygraphic recording (electroencephalography, electrocardiography, and measurement of respiratory movements) and transcutaneous oximeter monitoring. The diagnosis of Rett syndrome and autism was excluded as our patients did not fit the criteria proposed by Olsson and Rett.[3] All but one were severely mentally retarded with total absence of speech: only one girl showed a moderate mental retardation.

All our patients presented with hyperventilation. Interesting parallels were found with the cases of Rett syndrome of Southall *et al.* Prolonged apnoeic pauses or Valsalva manoeuvres, or both, occurred immediately after episodes of hyperventilation, sometimes resulting in a vagal syncope with consciousness impairment. Blood oxygen tension fell during breath holding and rose to normal values when respiration started again. Breathing was normal during sleep. A feeling of anxiety was experienced by all the observers when children hyperventilated and had prolonged apnoeas and self induced syncopes. The parents complained of the same feeling.

Five of our patients underwent measurement of their brain stem evoked responses that were elicited by monoaural clicks at 70 dB hearing level during active wakefulness; absolute and interpeak latency values were normal. We did not succeed in recording brain stem evoked responses in the sixth patient because of his behavioural disorder.

We believe that the results of measurements performed in the children we studied indicate that the respiratory abnormalities in brain damaged children with autistic traits do not differ from those of Rett syndrome. Thus the same mechanism could be implied. As brain stem evoked responses represent a device for investigation of brain stem function, the hypothesis that hyperventilation in these children results from a brain stem dysfunction is not supported by our findings. Reduction of the higher centres inhibition could be a possibility, but we believe that the adjunctive hypothesis, psychological rather than medical, should be considered.

Gastaut stated that self induced Valsalva manoeuvres could represent a behaviour reinforced from the pleasure obtained by the brief loss of contact with the surroundings.[4] We consider that breathing abnormalities and loss of consciousness evoke painful emotions in observers. The children we studied have very poor means of expression —with five out of six being totally speechless—thus the reported behaviour could be considered a psychotic means of communication of bad feelings.

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# Treatment of renal failure in neonates

Sir,

We are interested by the frequency with which renal failure is diagnosed and peritoneal dialysis prescribed in Manchester[1] as we have dialysed only two infants in the last 40 000 births: one with severe birth asphyxia and one with congenital heart disease, both of whom died. Six other infants in whom renal failure was present at the time of death were not dialysed because their primary condition (birth asphyxia or congenital abnormalities) was irremediable. We suspect that the difference lies at least in part in the criteria for diagnosis.

'Poor urine output' together with uraemia and hyperkalaemia do not necessarily constitute acute renal failure. All these are common in preterm neonates with normal renal excretory ability. The babies cited above are the only ones in whom we detected a significantly reduced glomerular filtration rate as indicated by a plasma creatinine concentration rising above 130 μmol/l. Creatinine measurement is an indispensible indicator of renal function. Although a single result for plasma creatinine may be difficult to interpret (both because of maternal influences and analytical interferences), a rising creatinine concentration is a useful indicator of functional renal decline. Moreover, the measurement of urine creatinine will distinguish between decreased renal perfusion and intrinsic renal failure. Low urine volume will occur with both.

The high plasma urea concentration, common in sick preterm infants, is caused by their hypercatabolic state with urea excretion rates up to 15 mmol/kg/day in our studies. Similarly potassium turnover is far higher in catabolic infants, and may exceed the capacity of the normal preterm kidney which can only filter 3 or 4 mmol/kg/day. It is not surprising that hyperkalaemia is common.

Our observed incidence of renal failure severe enough to require dialysis is in agreement with that of Brocklebank of 0·2/1000 live births.[2] Other infants may have had transitory renal impairment which was managed, without hazard, conservatively. Although Meeks and Sims do not mention the number of births their unit covers, their incidence of infants requiring dialysis does seem high.

While we would agree that peritoneal dialysis is a relatively straightforward technique, it is not without its hazards, and is no substitute for careful monitoring of renal function together with paying meticulous attention to the details of water and electrolyte balance. We believe that recoverable renal failure amenable to dialysis is uncommon. Moreover, in view of the long term neurological and renal consequences in the survivors of neonates receiving dialysis,[2] treatment should be approached with caution.

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# Clinical research group

Sir,

Clinical research is an integral part of training for the hospital doctor and experience in this field has become an important factor in securing senior registrar posts. Junior doctors with a busy clinical commitment may find it difficult to find time and motivation to undertake clinical research. With this in mind, a clinical research group was formed in Liverpool in 1985 to promote clinical research in paediatrics among junior doctors in the region.

The main aim of the group is to provide an informal forum to exchange ideas, discuss, promote, and improve the quality of clinical research in paediatrics. Doctors are encouraged to present hypotheses or ideas for research at an early stage of development after having formulated the idea into a written research protocol, but before having embarked on the project. The group discusses the proposed hypothesis and protocol and may make constructive criticisms and suggestions for alterations to the methodology. After completion of the project, presentation to the group affords a valuable opportunity for practice of a spoken paper before a critical audience before presentation to a scientific meeting.

Doctors who have previous experience in clinical research are invited to share their experience and lecture on research methodology and related subjects. Topics have included: the design and analysis of results from a clinical questionnaire, literature searching, design and running a drug trial, the use of a personal computer to run a research project, reviews of statistical software, and advice in planning an MD thesis. Guests are invited from staff within the hospital and university, to talk on selected topics requested by members of the group. Contributions on statistical analysis have been particularly well received. Members of the department of medical illustration have talked on the presentation of graphical material and artwork for publication and slides, and on the preparation of posters for scientific meetings.

Since the group was formed in 1985 the administration and organisation of the group has passed from one senior registrar to the next. The group has successfully promoted a wide interest in clinical research among junior staff.

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## Impact of AIDS on neonatal care

Sir,

I greatly enjoyed Tom Lissauer's annotation on the impact of AIDS (does he mean HIV infection?) on neonatal care.[1] I beg to differ, however, on his conclusion that we should avoid the 'two tier' system of neonatal care. At delivery, where there is much blood and liquor and the potential for staff to become infected (although none have yet been shown to have been infected at delivery), the Royal College of Obstetricians and Gynaecologists have not unreasonably proposed a general improvement in standards of hygiene, and extra precautions for delivery of women who are HIV seropositive or from high risk groups.[2] Their proposals regarding precautions to be taken by paediatric staff at delivery also seem eminently reasonable.

The risk to staff of contracting HIV infection from a baby postnatally, however, is exceedingly low and there may be virtually no risk. To suggest that we should be wearing gloves and eye protection whenever we are taking blood or performing any invasive procedure on any newborn must be an over reaction. Why should the risk stop in the newborn period? The corollary is surely that we should wear gloves whenever we take blood from any child, or adult for that matter. Yet, as Dr Lissauer himself states, the major risk is of accidental autoinoculation with HIV positive blood against which gloves provide very little protection. In many hospitals in New York gloves are worn for all procedures as Dr Lissauer's statement implies. The annual gloves bill for one hospital in the Bronx is over 5 million dollars (A Mezey, personal communication). I think this is illogical, expensive, and off putting to parents and children. I believe staff with open lesions (cuts, eczema) should cover these with waterproof tape. I will wear gloves to take blood from babies and children I know to be, or suspect of being, HIV positive and try to avoid needle stick injuries at all times. But I will not wear gloves and eye protection to take blood from or handle other newborns or older children.

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## Bradycardia associated with chlorhexidine spray

Sir,

We report a possible iatrogenic cause of bradycardia in a term neonate.

### Case report

The girl was born by normal delivery after an uneventful antenatal period. Her Apgar scores were 9 and 10 at 1 and 5 minutes respectively. No medication was given during the labour. In order to prevent possible mastitis the mother used chlorhexidine spray on her breasts from the third feed when the baby was 12 hours old. Cyanotic spells associated with bradycardia (<40 per minute) but not with apnoea occurred from 48 hours. The heart rate was lowest during sleep but increased on stimulation. Multiple episodes occurred over the next 48 hours, and some needed treatment with atropine, to which they responded. An electrocardiogram confirmed sinus bradycardia. The chlorhexidine spray was stopped and the bradycardias became less frequent and less severe. By day six they had abated completely and follow up examination at five weeks was normal. Investigations including full blood count, urea and electrolytes, thyroid function tests, cardiac enzymes, and an echocardiogram were all normal. The serum chlorhexidine concentration at 120 hours was 11 pg/l. This was estimated when the spray had been stopped and the worst of the bradycardias had abated.

Adrenergic nerve damage, which was dose dependent but reversible, has been produced in rat irides after the local injection of as little as 0·25 µg of chlorhexidine.[1] The gastrointestinal absorption of chlorhexidine has not been studied in man but assumed to be low[2] despite studies showing significant absorption through the intact skin of newborn infants.[3] The dose of chlorhexidine in each spray is 430 µg. Over 24 hours (assuming six feeds) 2·5 mg is delivered to the breast and could be ingested by the baby. Studies on absorption of chlorhexidine from the gastrointestinal tract need to be conducted and awareness of possible side effects maintained.

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## Measles immunisation in atopic eczema

Sir,

Last year a communication from the Department of Health and Social Security indicated that there was an upsurge of measles notifications in early 1988 and emphasised that allergy to hens' egg is no longer considered to be a contraindication to measles immunisation unless associated with an anaphylactoid reaction.[1] This specific contraindication also applies to the MMR vaccination.[2]

In 1984/1985 we performed a questionnaire study of all children with atopic eczema who had attended a dermatology clinic at the Hospital for Sick Children, Great Ormond Street, at any time in the previous four years. Questionnaires were also answered by non-eczematous controls matched for age and social class. There was an 82·7% response with 128 cases and 117 controls out of a total of 148 pairs of questionnaires. Measles immunisation had been withheld for inappropriate reasons from 28·9% of the eczematous children and 2·6% of controls.

Although this questionnaire response reflects attitudes among health professionals in the early 1980s it is our impression that a considerable number of atopic children, particularly those with atopic eczema and those with a vague and unsubstantiated history of egg allergy, are still inappropriately denied immunisation. Approximately 10% of children will experience atopic eczema at some stage in their childhood and there is evidence that this is increasing.[3] Uncertainty in the profession as to the contraindications to immunisation in this group may adversely affect the immunisation rate for the population as a whole. We welcome the latest attempts by the Department of Health and Social Security to clarify this issue.

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# *Neonatology—then and now* (*C H M Walker*)

## Monitoring blood oxygen (1957)

# Blood oxygen studies in premature infants

PATRICIA M RUSSELL AND F P HUDSON

*Walton Hospital and Department of Child Health, University of Liverpool (Arch Dis Child* 1957;**32**:392–6)

In the early 1950s there was some debate as to whether the lower and variable oxygen *saturations* observed in premature babies were of importance and whether or not they required correction. The observation that the irregular (periodic) respirations of premature babies became regular when they were given oxygen was observed personally (CHMW) even in babies born at full term in the Mile High City of Denver, Colorado. The respiratory mechanisms of some of the latter apparently respond to the lower ambient partial pressures of oxygen at altitudes of 5000 feet just as do preterm babies at lower altitudes.

The purpose of this study was therefore to measure the effect of administering 55–60% oxygen to premature babies for one hour. The birth weights of these babies were not given but it is presumed that they were below 2500 g. While $PO_2$ 'in the lung' (presumably alveolar air) was used in calculations of dissolved oxygen, arterial $PO_2$ could not be measured in small volumes of blood and all estimations in those days were in terms of percentage saturation and content in volumes percent. As might be expected increases in saturation (up to 105%) and content (up to 31 volumes %) were observed even with as little as 55–60% oxygen.

But there was an interesting conclusion:

> 'There was, however, no indication that prolonged oxygen therapy was needed by any of the infants at the time they were being studied. It is unlikely that the routine study of blood oxygen levels of healthy premature babies would assist in their general management.'

This is not to say that vigilance was disregarded but gone are the days (not that we ever had them in the United Kingdom) when one saw as I did in 1964 in the 'preme' nursery of the celebrated Clement Smith in Boston, a nurse sitting at almost every incubator watching for signs of apnoea and hypoxia.

**Today** It is intriguing to find that after many years of being 'lost in the wilderness' oxygen saturation, now measured by means of the pulse oximeter, has returned as an additional means of controlling oxygen treatment.[1] The technology for the measurement of oxygen saturation in babies by surface oximetry was, of course, quite far advanced even in the 1950s but seemed to be overtaken by that of partial pressures and 'laid aside'. But how attitudes to monitoring have changed. Indeed, the conclusion of this 1957 paper is rather strange because the link between retrolental fibroplasia and oxygen treatment had already been recognised. It is likely, however, that most babies who weighed less than 1500 g at birth died, and many of the more mature who survived were indeed 'healthy'.

The problem today is seldom one of administering too little oxygen but rather of exposing the infant to too much. Despite the wonders of modern monitoring equipment, wide fluctuations cannot be totally avoided: sudden blockage or displacement of tubes, pneumothoraces, segmental collapse, and so on, must expose the infant even temporarily to fall and rebound in oxygen supply to brain, eye, gut, and myocardium—all of which react in their own way.

Hindsight makes it easy to criticise but, of course, we now regard monitoring blood gases as essential management, though unfortunately in the 'healthy' preterm baby it is now almost as much for medicolegal protection as it is for the benefit of the baby. Are the frequent assays now performed always necessary and in the best interests of infants who require frequent 'top up' transfusions caused at least in part by iatrogenic blood loss?[2]

Unfortunately non-invasive methods have come to our rescue only to a limited extent, and the wide ranging biochemical monitoring now practiced will be with us for a long time to come. So frequent 'top up' transfusions—that are not entirely free from haemodynamic or infectious complications—will continue. As long as litigation hangs over the head of the neonatologist frequent blood oxygen (and other) measurements in preterm infants, healthy or otherwise, will remain mandatory.

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Frederick Hudson qualified in Glasgow (1937) and after early hospital appointments in England served as a medical specialist in the Royal Army Medical Corps during the second World War. After demobilisation he became clinical tutor at the Royal Hospital for Sick Children in Edinburgh and in 1947 was appointed consultant at the Alder Hey, Royal Liverpool Babies' and Walton Maternity Hospital, and later Clinical Tutor in Child Health at the University of Liverpool. He established a special care baby unit at the Walton and his studies and publications included work on oxygen saturation, Vitamin K, convulsions, and galactosaemia. He had a particular interest in metabolic disorders and as well as starting a children's diabetic clinic at the Alder Hey he became director of the Medical Research Council/Department of Health and Social Security Phenylketonuria Registry (UK) and founder member and later president (1972–74) of the Society for the Study of Inborn Errors of Metabolism.

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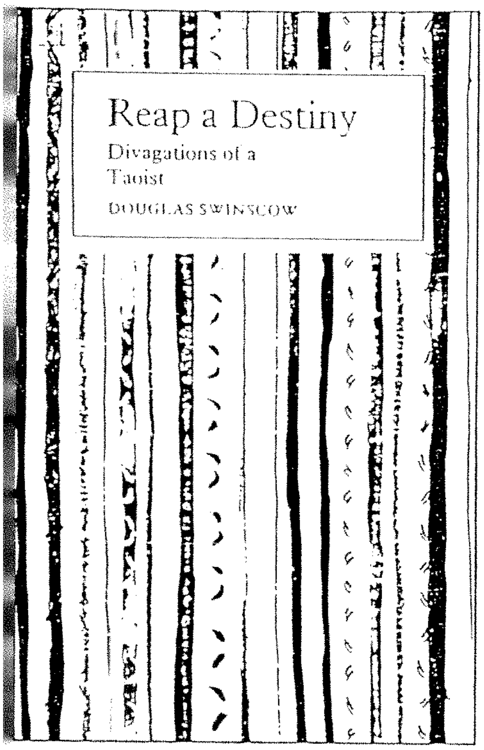

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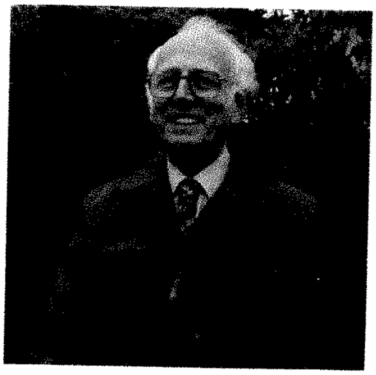

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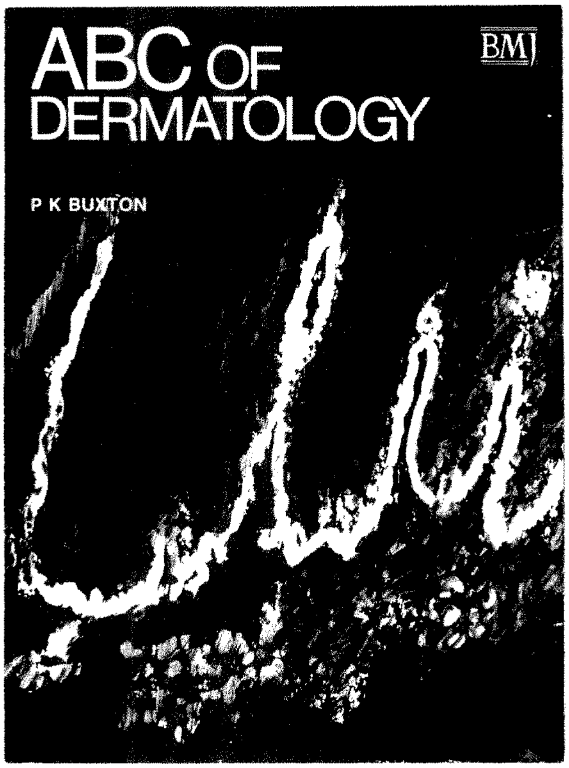

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## *Annotations*

# Group A streptococci revisited

In the first half of this century group A streptococci were one of the most important of all bacterial pathogens, causing large outbreaks of scarlet fever with a high mortality, puerperal fever and neonatal sepsis, rheumatic fever and glomerulonephritis as well as suppurative conditions such as empyema, osteomyelitis, and septic arthritis. Time and penicillin have assuaged our fear and replaced it with complacency.

Recently, however, there have been increasing reports to the Public Health Laboratory Service of severe and sometimes fatal episodes of sepsis caused by group A streptococci. What sets this organism apart from other pathogenic bacteria is its potential to cause delayed, non-suppurative complications, namely rheumatic fever and glomerulonephritis. The decline of rheumatic fever in developed countries was never satisfactorily explained and recent reports from widely separated locations in the United States suggest the disease may be resurgent.[1 2] The old lessons of epidemiology and treatment are having to be re-emphasised for a new generation of physicians.

### The organism

*Streptococcus pyogenes* (Lancefield group A) is a Gram positive coccus. The cell wall is composed mainly of carbohydrate, the antigenic properties of which determine the (Lancefield) group specificity. The cell wall is surrounded by a layer of hyaluronic acid which gives colonies a mucoid appearance. The recent outbreaks of rheumatic fever in the United States have coincided with the appearance of more mucoid strains.[3] Hair like fimbriae containing lipoteichoic acid project from the cell wall and are responsible for adherence to epithelial cells. Over 60 different strains can be differentiated on the basis of serologically distinct M proteins, associated with the fimbriae. Certain M proteins confer resistance to phagocytosis and increase virulence.[4] Associations are recognised between certain M proteins and diseases such as pharyngitis and impetigo.

Group A streptococci manufacture and release a variety of biologically active substances. Two haemolysins are produced, streptolysins O and S, which can damage cell membranes and subcellular membranous organelles and thus are toxic to polymorphonuclear leucocytes, lysosomes, and platelets as well as red blood cells. Streptolysin O is antigenic and antistreptolysin O (ASO) antibodies are a useful marker of recent infection. An erythrogenic toxin is produced by some strains and is responsible for the rash of scarlet fever.[5] Other extranuclear products are enzymes which may facilitate the formation of pus and the spread of infection through tissue planes. These include enzymes that degrade deoxyribonucleic acid (DNAases, A, B, C, and D) and streptokinase that promotes the breakdown of clot. Antibody against DNAase B has also been used in the serodiagnosis of streptococcal infection.

### Streptococcal sore throat

The most common clinical expression of group A streptococcal infection in developed countries is pharyngitis and tonsillitis. The need to diagnose and eradicate the streptococcus in order to prevent suppurative complications (otitis media, sinusitis, peritonsillar, and cervical abscess), later non-suppurative complications, and spread within the community has dictated hard learnt rules of treatment and stimulated a search for rapid diagnostic kits for the 'strep throat'. Streptococcal tonsillitis occurs predominantly in school age children and has a rate of recurrence of one infection every three to five years during childhood. Older age groups are, however, susceptible, particularly in situations of overcrowding such as military camps, prisons, and remand centres.[6] After an incubation period of one to four days there is an abrupt onset of illness with sore throat, malaise, fever, and headache. It is often accompanied by nausea, vomiting, and abdominal pain. The tonsils and pharynx are inflamed. A greyish white exudate on the tonsils is common but not invariable.[4] Tender lymph nodes are palpable at the angle of the mandible. A range of severity exists, however, and illness can be deceptively mild. The natural history is for symptoms to subside within three to five days unless suppurative complications intervene. The average latent period for the development of acute glomerulonephritis is 10 days and for rheumatic fever 18 days.[7] After recovery from pharyngitis neutralising type-specific antibody does not develop for six to eight weeks, but then confers resistance to subsequent infection by that serotype. Exudative pharyngitis below the age of 3 is hardly ever due to group A streptococci, although infected infants can develop an illness characterised by low grade fever, lymphadenopathy, and rhinorrhoea.

Close contact favours the spread of streptococcal pharyngitis by large droplets or by physical transmission of respiratory secretions.[6] Children are most infectious during the acute phase of the illness. Most secondary spread occurs within the first 14 days after acquisition.[8] Up to 20% of children carry group A streptococci in the throat and are without symptoms or subsequent evidence of an immunological response (carrier state). The role of carriers in the spread of infection is controversial: they appear less likely to transmit the organism than acutely infected patients and are at significantly reduced risk of developing rheumatic fever.[9]

The diagnosis of streptococcal sore throat on clinical grounds alone is unreliable.[10] Throat culture is the 'gold standard' of diagnosis against which newly developed rapid diagnostic tests have to be judged. Approximately one third of those complaining of sore throat will have a throat culture positive for streptococcus.[11] Some of these will be carriers with another intercurrent infection responsible for their symptoms. Does accurate diagnosis matter? Why not treat all children with sore throat with penicillin regardless of a throat culture? It is debatable that penicillin makes much difference to the acute illness. A recent double blind controlled trial of penicillin and regular anti-inflammatory treatment compared with placebo and regular anti-inflammatory treatment showed no significant improvement in malaise, fever, adenitis, or pharyngitis in the penicillin group.[12] Penicillin, however, does reduce the acute complication rate and eliminates pharyngeal streptococci thus reducing the risk of rheumatic fever and preventing transmission.[13] Elimination of pharyngeal streptococci depends on prolonged rather than high dose penicillin treatment. With reduction in rheumatic fever rates the use of unpleasant intramuscular injections of long acting benzathine penicillin went out of vogue. The alternative, oral penicillin V, must be continued for a full 10 days.[14] Even the most compliant child or parent finds it difficult to complete a full course especially when symptoms have abated. A throat culture should be taken so that culture negative patients could stop penicillin after 48 hours while a positive culture would allow reinforcement that the course of penicillin should be completed. Rheumatic fever may be preceded by a mild illness or even asymptomatic infection.[1] An accurate diagnosis of streptococcal pharyngitis is important when cases of rheumatic fever are rare, but vital if rheumatic fever is epidemic. Treatment of a streptococcal sore throat as late as 10 days after onset will prevent rheumatic fever.[15]

## Rapid diagnostic tests

The development of rapid diagnostic tests for group A streptococci was greeted with enthusiasm as a way of knowing within an hour of taking a throat swab which patients to treat. This has been tempered by doubts as to their accuracy. They rely on the extraction of the group specific carbohydrate from the cell wall and its recognition by agglutination. False positive results are not a problem. Facklam, in a recent review of the literature, found specificities of ≥95% in 75% of kits tested.[16] False negatives are of more concern. Facklam found 44% of kits had sensitivities of ≤85%, some as low as 60%, and less than 40% had sensitivities ≥90%. The false negatives often correlate with throat cultures showing only scanty growth of bacteria. This would be bearable if the false negatives represent carriers where a small amount of antigen is present, but Gerber *et al* suggest otherwise.[17] They found that a third of individuals with false negative rapid antigen detection tests had a subsequent rise of streptococcal antibody titres suggesting infection. Summarising a decade since the introduction of rapid streptococcal diagnostic kits into commercial use, Kaplan suggests that a positive result indicates with relative certainty that streptococcal antigen is present but when negative a confirmatory throat culture is prudent.[18]

## Other clinical manifestations

Impetigo caused by group A streptococcus is common in tropical and subtropical countries. The bacteria initially colonise unbroken skin and cause lesions an average of 10 days later possibly via surface abrasions or insect bites.[19] Impetigo may be followed by acute glomerulonephritis but not, interestingly, rheumatic fever. Bacteraemia with group A streptococci is usually associated with a focus of infection, most often the skin or respiratory tract,[20] with varicella,[21] or in immunocompromised patients. Infections can be severe with significant mortality.[20] Streptococcal pneumonia may follow preceding viral infections such as measles and influenza but can also be primary and occur in outbreaks.[22] A third of cases are associated with empyema. Metastatic foci may follow bacteraemia, including osteomyelitis, septic arthritis, and meningitis.[20]

## Rheumatic fever

In Britain the number of cases of rheumatic fever has fallen in parallel with other western countries. The incidence fell from five cases per 100 000 population in 1963 by at least 10 fold by 1985 (ND Noah, S Hall, Communicable Diseases Surveillance Centre, personal communication). These figures are based on the Hospital Inpatient Enquiry, a 10% sampling of hospital discharges and deaths. When a disease becomes uncommon these figures may not be a true reflection of incidence. To overcome this, the British Paediatric Surveillance Unit (BPSU) performed a 'one-off' retrospective enquiry for 1987 the data from which are still being analysed. It is hoped to put acute rheumatic fever on the BPSU monthly reporting system this year. The explanation for falling rates of rheumatic fever was never clear. Improved living conditions with lessening of malnutrition and of overcrowding do not explain the change over the last 20 years when decline of rheumatic fever has been the greatest. It is of interest that the recent American outbreaks have affected white, middle income, suburban families. While the assiduous use of throat culture and penicillin in populations at risk probably reduces rates of rheumatic fever[23] overall rates were falling before the introduction of antibiotics and continued to fall recently when patterns of antibiotic use did not change. A change of streptococcal virulence has been suggested. Certainly scarlet fever in England and Wales has shown a considerable decrease in both incidence and severity in this century[24] but there is nothing to suggest that streptococcal sore throat is a declining disease. The search for 'rheumatogenic' strains of streptococci has been unsuccessful. Even though only 25% of rheumatic fever patients will have streptococci isolated from the pharynx at the time of presentation a careful study of those strains found in patients and their sibling contacts from the recent outbreaks in the United States showed that several different serotypes were responsible even within a specific geographic location.[3] Host factors, such as rheumatic fever sufferers possessing a particular B cell alloantigen,[25] do not adequately explain rapid changes in incidence of disease.

## Conclusion

Group A streptococci remain important and serious pathogens. Vigorous detection and treatment of the streptococcal sore throat is to be encouraged. The recognition and accurate reporting of rheumatic fever and the characterisation of group A streptococci isolated from these patients should be emphasised so that, if a return of rheumatic fever is upon us, it can be understood better than its previous decline.

My thanks to David Isaacs, Dick Mayon-White, and Richard Moxon for advice.

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# Research in community child health

The Community Paediatric Group is the largest specialty group within the British Paediatric Association. The Group is growing, as is the number of consultants in the specialty, and the numbers of doctors in approved training posts. Since the publication of the *Court Report* in 1976, there has been a large increase in interest in the specialty, developments in terms of structure and process in the service, and an air of questioning the premises and practice of community paediatrics. In this atmosphere, it would be expected that the pages of journals such as this should be filled with good research in community child health. The reality is that this is not so, both in terms of volume and quality. This article attempts to explore some of the reasons for this and to recommend some solutions.

## Problems

Much decision in community paediatrics has, I fear, been based on what one might call 'the biblical method of assessment', that is, 'they looked at it and saw that it was good.' This may have been adequate for our most distant ancestors but today would satisfy neither general managers, academic departments of paediatrics, or the editors of journals. The specialty has developed rapidly, sometimes running ahead of our knowledge.

An academic priority over the last few years has certainly been training. A survey from the Department of Health and Social Security in the mid 1970s showed that 75% of the full time doctors in community child health, and 85% of the part time doctors, had had less than six months training in paediatrics. The task, therefore, for many people, was to get existing knowledge into the heads of those who needed it and setting up training programmes, rather than expanding the volume of knowledge. The rapid service development has increased training demands as has responsibility for new tasks, such as work within child sexual abuse.

New senior registrar posts in community paediatrics have been created. Their numbers are not yet sufficient to meet the future needs for consultants in the specialty and their content often does not permit as much research time as would be allocated in an equivalent hospital senior registrar post. We are again troubled by the large service need. While hospital consultant posts in paediatrics, and supporting posts, increased by around 50% from 1975 to 1985, there has been little change in the staffing levels in community child health. It is certainly extremely difficult to take on new clinical tasks and to set up training posts, where time is needed for teaching and clinical supervision, as well as setting up ambitious research projects at a time when establishment has not risen. Posts have even been frozen to enable health authorities to balance their budgets.

Community paediatrics is not established in all academic departments of child health. This clearly imposes a limiting factor upon the promotion and supervision of research.

In its recent history, community child health has attempted to separate itself from community medicine and has aligned much of its professional and training structure with paediatrics. Although this can be seen as a necessary step in the development of community paediatrics, it has also lost the links with departments of community medicine who may well have the epidemiological skills necessary for many studies in community paediatrics.

Lastly, there are many methodological problems in terms of research which looks at whole populations as opposed to individuals with a defined medical diagnosis. There are numerous traps waiting for the unwary researcher in community paediatrics.

## Some suggested solutions

More training posts in community child health are needed. These should include research time and adequate supervision of the research. Training in paediatric epidemiology would be a great asset for some of the senior registrars.

Expansion of academic posts in community paediatrics is needed. The first Chair of Community Child Health has recently been appointed at the Royal Free Hospital. The need for research clearly must be matched with the availability of research money. Specific research funds for community child health has not yet developed and sometimes the low profile of prevention, health promotion and surveillance makes it difficult for community paediatrics to compete for research funds with other specialties. Research money from commercial sources is also more difficult to attract.

Researchers in community child health would do well to dip into the experience of other specialties and to look at mutual areas of interest to set up joint areas of research. Examples would be community medicine, psychology, sociology, pharmacy, education, nursing, and administration.

The Community Paediatric Research Group started life in 1978. These meetings and those of the Community Paediatric Group have provided the main national forum for presenting research in community paediatrics to a critical audience, and to organise seminars that can discuss issues related to research methodology. In some districts, funds for study leave for doctors in community child health are not available to enable doctors in training to attend relevant academic meetings.*

## Some suggested targets for research in community child health

This represents a personal shopping list of research that I would like to see done in community child health. It is not intended to be complete.

### OUTCOMES AND EFFECTIVENESS OF CHILD HEALTH SURVEILLANCE PROGRAMMES

Long term outcomes need to be looked at, as well as the effectiveness of initial identification procedures. Mortality and morbidity from disorders at which surveillance programmes are aimed, should also be examined. Much of our current surveillance programmes remain unsupported by any objective evidence.

### INTERVENTION STUDY WITH DISADVANTAGED POPULATIONS

Cycles of disadvantage are well described but there are a lack of studies indicating the effectiveness of the services that we provide for these populations. These families are frequently the focus of intense health visitor and community paediatric involvement, and of innovative educational and other projects, but we know little about the effectiveness of these services.

### DISTRICT HANDICAP TEAMS

Most districts now have a district handicap team with considerable involvement from community child health. Their working practices vary widely and there is little research to guide us into which model of service we should be favouring for the future.

### INTERDISCIPLINARY WORK

Our effectiveness, or so it is believed, in community paediatrics depends upon good interdisciplinary work with a wide variety of other professions. Our failings, where they have been pointed out, for example, in enquiries, frequently indicate a lack of interdisciplinary working. The examination of interdisciplinary working in a wide range of issues in community paediatrics from child health surveillance through to management of handicap or child abuse, would be a valuable contribution to our knowledge.

### HEALTH EDUCATION/HEALTH PROMOTION

These form a major activity within community child health. We are, however, often uncertain about the effectiveness of the programmes which we carry out.

### USE OF SERVICES BY PARENTS

A total of 90% of illnesses are dealt with by parents rather than professionals. Hospital admission rates for children are rising. Parents are often more likely to bring their child to the accident and emergency department rather than to see the general practitioner. Our workload is governed by the decision making of parents, and the relative roles of services for prevention and services for treatment need to be examined.

### THE SCHOOL HEALTH SERVICE

The school health services have existed since the beginning of this century. The pattern of services is changing from routine examination towards being more selective, to place more emphasis on health promotion and to expand the liaison role of the doctor. In many cases, we lack information about the operation of the school health services. With the 1981 Education Act, it is recommended that more children with special needs are placed in ordinary schools. It has been assumed that they will be better off, but studies aimed at looking at children with special needs in ordinary school, who might otherwise have attended a special school, would be most welcome.

### INFORMATION SYSTEMS

Hospitals produce audit information on admissions and discharges. Community paediatrics needs information too, on its day to day activities and on the nature and distribution of handicaps within the community. We are only just beginning to do this. It is difficult sometimes for a service to march forward when it does not know exactly where it is at present.

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## Conclusions

At such a time of rapid expansion, there are opportunities for research which must be taken before the pattern of service delivery solidifies and becomes impossible or difficult to change in the light of research findings. Every doctor in community paediatrics should have an opportunity, and the responsibility, to think about what they are doing, to ask questions and hopefully to obtain answers. Academic departments have the responsibility to nurture and help research in community paediatrics. Research funds need to be made available for this to be done. The National Health Service needs to support research and to plan for adequate manpower and training programmes to ensure that this can be done.

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## *Original articles*

# Early markers of the renal complications of insulin dependent diabetes mellitus

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SUMMARY We investigated the associations between albuminuria, metabolic control, glomerular filtration, blood pressure, and platelet function in children with insulin dependent diabetes mellitus. The geometric mean (95% tolerance levels) albumin excretion (expressed as the geometric mean albumin to creatinine ratio on two overnight urine collections (UA/UC)), in 60 diabetic children was 0·72 (0·80–6·9) mg/mmol, significantly greater than in 45 normal children (geometric mean 0·41(0·14–1·17)). Mean (SD) glomerular filtration rate, measured by $^{51}$Cr edetic acid clearance during constant infusion, was significantly greater in diabetic children (129 (20) ml/min/1·73 m$^2$) compared with normal controls (109 (13)). Mean (SD) renal length for height standard deviation score was +0·25 (1·1); systolic blood pressure standard deviation score was 0·15 (0·65), and diastolic blood pressure was 0·51 (0·82). Spontaneous platelet aggregation, expressed as percentage fall in platelet count in stirred whole blood after 2 minutes was 17·8 (9·2)% in the diabetic compared with 12·3 (7·9)% in normal children. UA/UC correlated with renal length and of the children with UA/UC above the normal range, 70% also had a glomerular filtration rate above the normal range. There was a weak correlation between UA/UC and glycated haemoglobin (HbA$_{1c}$). All children with spontaneous platelet aggregation above normal had had diabetes for more than seven years. These cross sectional data define some of the early markers and inter-relationships that may be important in the development of nephropathy.

The risk of developing nephropathy is highest in those individuals with insulin dependent diabetes mellitus (IDDM) in whom the disease starts in childhood,[1 2] but it is difficult to identify accurately the susceptible individuals in the early years. The only marker that has been shown in prospective studies of adult diabetic individuals to predict nephropathy is the presence of microalbuminura.[3–6] This predates the onset of 'macroproteinuria', decline in glomerular filtration rate, and onset of hypertension.[7] The level of urine albumin excretion, however, which best predicts nephropathy remains unclear as studies have varied in their methods of urine collection and attention to variability, which is high in both normal and diabetic individuals.[8–10] Microalbuminuria, defined as urine albumin excretion above the 95th centile for normal children has been reported to be raised in 12–20% of diabetic children.[11–14]

Other possible early markers of nephropathy in diabetes include an increase in glomerular filtration rate, kidney size, and blood pressure. A high glomerular filtration rate has been reported in 20–30% of diabetic children under conditions of standard insulin treatment,[14–16] and although poorly studied in childhood, increased renal size has been described in adults with IDDM, both at diagnosis and during the early years of the disease.[17–19] Hypertension is an accepted feature of diabetic nephropathy after the appearance of microalbuminuria and its treatment has been shown to slow the decline of renal function.[20 21] In children with IDDM, blood pressure data are conflicting, but where increases have been shown, they have been small.[22–24] A problem in most of these studies is the choice of controls. Some studies have used the siblings of the diabetic children,[22] whereas others have related the results to normal published data.[13] At present there are no such data for British children and it is necessary to use either continental[25] or American data.[26]

Abnormal platelet function has been implicated in the pathogenesis of diabetic, nephropathy,[27 28] and increased platelet aggregation has been reported in children with IDDM in the early stages of the disease.[29]

Weak correlations between some of these markers have been reported in previous studies,[11 13 30] but they have not been systematically described together in a population of children with IDDM. We have therefore examined the associations between them and urine albumin excretion in order (a) to determine whether a single population of diabetic children share these possible risk factors and (b) to examine the role of other compounding factors such as age, puberty status, metabolic control, and duration of disease.

## Subjects and methods

### DIABETIC SUBJECTS

Sixty children and adolescents attending the diabetic clinics at the Hospitals for Sick Children, London, agreed to participate in the study. Their mean (SD) age was 13·1 (3·5) years and the mean duration of IDDM was 7·0 (4·3) years; 16 (27%) of the children were prepubertal, 17 (28%) in early puberty (stages 2 and 3), and 27 (45%) were in late puberty (stages 4 and 5); there were 27 boys and 33 girls. Two of the 60 diabetic children were on anticonvulsant drugs (carbamazepine and sodium valproate). The remainder were receiving no other drugs apart from insulin. None of the diabetic children or controls had taken aspirin during the preceding two weeks and none of the children had evidence of urinary infection at the time of study.

Complete studies were undertaken on all 60 children with the exception of glomerular filtration rate measurement; only 44 children agreed to this procedure.

### CONTROLS

The urine albumin excretion was measured in 45 normal schoolchildren of mean age 13·4 (2·7) years; nine (19%) were prepubertal, 14 (32%) in early and 22 (49%) in late puberty; there were 23 boys and 22 girls.

Platelet studies were undertaken in 26 normal children of mean age 13·1 (4·9) years before minor surgery; blood samples were taken at the same time as the routine check for haemaglobin concentration.

It was not possible to obtain control data for glomerular filtration rate measurements in normal children. As glomerular filtration rate corrected for surface area reaches adult values by the age of 2 years,[31] however, it was considered justifiable to use adults as controls. Glomerular filtration rate was measured in 15 normal young adults, mean age 24·1 (16·5) years who were recruited from hospital staff and friends; there were seven men and eight women.

All of the studies described had the approval of the ethical committee at the Hospital for Sick Children, Great Ormond Street, London.

### METHODS

### *Urine albumin excretion*

We measured urine albumin excretion on overnight urine samples because the variability is less than in 24 hour or daytime collections[9 32] and they are more practical to collect at home. The duration of overnight collections was similar in normal and diabetic children.

Urine albumin concentration was measured by double antibody radioimmunoassay (Diagnostic Products Corporation) with a sensitivity of 0·5 mg/l, an intra-assay coefficient of variation of 4%, and interassay coefficient of variation of 5%. Urine creatinine concentration was measured by the Jaffé reaction and urine albumin excretion was expressed as the geometric mean urine albumin creatinine concentration ratio (UA/UC) in mg/mmol of two consecutive overnight urine samples. We have previously shown that overnight UA/UC correlated well with albumin clearance and urine albumin excretion rate.[8]

### *Glomerular filtration rate*

Glomerular filtration rate was measured using a constant infusion of 51-chromium ethylene-diamine-tetra-acetic acid ($^{51}$Cr edetic acid) under conditions of water diuresis. We used this technique because the unicompartmental plasma clearance method usually used for measuring glomerular filtration rate in children overestimates normal and high glomerular filtration rate and is therefore inappropriate for investigating hyperfiltration states.[33 34] All measurements were performed in the morning. Diabetic children had their normal morning insulin and all subjects were instructed to omit tea, coffee, meat, and milk for their breakfast meal; two to three hours later a diuresis was established with an oral water load of 20 ml/kg body weight. The mean (SD) urine flow rate in the diabetic children was 11·0 (3·5) ml/min and in the controls was 12·6 (4·0) ml/min. A priming dose of $^{51}$Cr edetic acid (0·025 MBq/kg) was administered, followed by a constant infusion of $2{\cdot}3\times10^{-4}$ MBq/kg/minute. After 45 minutes for equilibration, three or four carefully timed, spontaneously voided urine samples were collected at 20–30 minute intervals. A blood sample was drawn from a peripheral vein at the midpoint of each collection period. The mean of three or four clearances (UV/P) was then calculated and corrected to 1·73 $m^2$ surface area using the Dubois formula. Estimates of glomerular filtration rate were rejected if one or more individual clearance differed from the mean by more than 15%. Acceptable estimates of glomerular filtration rate were obtained in 41 of the 44 children studied.

### *Renal size*

Renal length was measured by ultrasonography with the child in the prone position and related to normal data for right and left kidney lengths plotted against body height.[35] Data on the diabetic children was expressed as the mean of the right and left kidney length standard deviation scores, compared with these normal published sonographic growth charts.

### *Blood pressure*

Blood pressure was measured in the right arm with the child seated, using a random zero sphygmomanometer with the appropriate sized cuff and taking the fifth sound as the diastolic blood pressure. All measurements were taken by the same observer after the glomerular filtration rate measurement was completed. Results were expressed as a standard deviation score related to the 1987 Task Force Data for blood pressure in normal children.[26]

### *Platelet aggregation*

Platelet aggregation was measured in whole blood using the Ultraflo 100 Whole Blood Platelet Counter. A total of 5 ml blood was taken into a polypropylene syringe using a 19 gauge needle and immediately transferred into a polystyrene tube containing 0·5 ml 3·8% trisodium citrate dihydrate. A 0·5 ml aliquot was then stirred in a plastic tube at 1000 rpm at 37°C. At 1, 2, 3, 4, and 8 minutes after stirring had commenced, 20 μl aliquots were taken and immediately fixed by mixing with 40 μl of formalin-edetic acid solution to prevent further aggregation or disaggregation before counting. Aggregation was expressed as the percentage fall in platelet count at 2 minutes compared with the count in an aliquot taken immediately before stirring.[36] All experiments were performed between one and three hours after venepuncture and a control was included in every platelet aggregation experiment.

### *Glycated haemoglobin*

Glycated haemoglobin ($HbA_{1c}$) was measured by an electrophoretic method, the normal range being 5·0–8·0%.

### STATISTICAL METHODS

Computation and statistical analysis was performed using the Statistical Analysis System (SAS Institute Inc). UA/UC in both normal and diabetic children was best described by a log normal distribution and therefore results were log transformed before analysis and expressed as the geometric mean and 95% tolerance limits (antilog −2 SD to +2 SD).[8] Comparisons of variables between normal and diabetic children and diabetic children with high versus normal UA/UC were made by use of unpaired (two tailed) Student's *t* tests. Associations between variables were examined using linear regression by the least squares method, Pearson's correlation coefficients, $\chi^2$ analysis, and multiple regression.

## Results

### PRIMARY DATA

Mean (SD) $HbA_{1c}$ concentration was 11·8 (2·3)% and correlated with increasing age (r=0·44, p<0·001).

The geometric mean (95% tolerance limit) for UA/UC in the diabetic children was 0·72 (0·08–6·9) mg/mmol, significantly greater than that of the normal children, 0·41 (0·14–1·17, p<0·001) and 15 (25%) of diabetic children had UA/UC values above the normal range (fig 1). The characteristics of these 15 diabetic children with high UA/UC are shown in table 1.

Mean (SD) glomerular filtration rate in the diabetic children (41 studied) was 129 (20) ml/min/

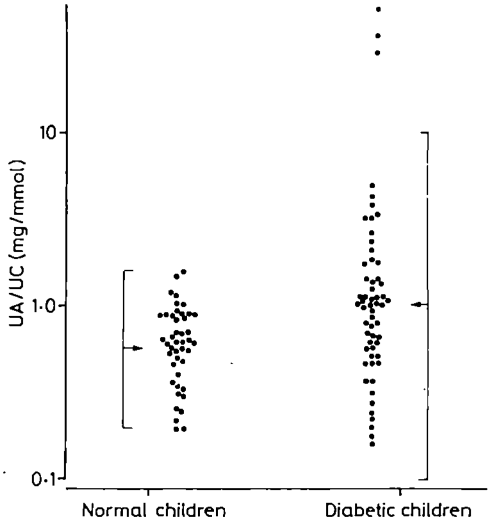

Fig 1 *Geometric mean and 95% tolerance limits for UA/UC in mg/mmol plotted on a log scale in normal and diabetic children.*

Table 1 *Comparison of diabetic children with high compared with normal UA/UC. Results expressed as mean (SEM)*

| *Variable* | *High UA/UC. (n=15) (>1·17 mg/mmol)* | *Normal UA/UC (n=45) (≤1·17 mg/mmol)* | *p Value (t test)* |
|---|---|---|---|
| Sex (M/F) | 5/10 | 22/23 | |
| Age (years) | 14·5 (0·73) | 12·7 (0·53) | <0·1 |
| No at puberty stage: | | | |
| 1 | 3 | 13 | |
| 2 and 3 | 2 | 14 | |
| 4 and 5 | 10 | 18 | |
| Disease duration (years) | 8·10 (0·92) | 6·80 (0·65) | <0·5 |
| Glycated haemoglobin (%) | 13·40 (0·53) | 11·20 (0·31) | <0·001 |
| Glomerular filtration rate (ml/min/1·73 m$^2$) | 140·10 (3·36) | 124·80 (3·65) | <0·01 |
| Renal size standard deviation score | 1·16 (0·28) | −0·03 (0·15) | <0·001 |
| Systolic blood pressure standard deviation score | 0·03 (0·06) | 0·19 (0·10) | <0·2 |
| Diastolic blood pressure standard deviation score | 0·59 (0·23) | 0·48 (0·12) | >0·5 |
| Platelet aggregation at 2 minutes | 18·80 (2·45) | 17·40 (1·36) | >0·5 |

1·73 m$^2$ surface area, significantly greater than the 109 (13) (p<0·001) observed in controls, and 16/41 (39%) had values above this normal range (fig 2).

The mean (SD) systolic blood pressure standard deviation score in the diabetic children did not differ significantly from zero (0·15 (0·65), 0·1>p>0·05), whereas the diastolic standard deviation score was significantly raised with reference to the normal published data (0·51 (0·82), p<0·001).

Renal size was also normal in the diabetic children with a mean renal length for child height standard deviation score of +0·25 (1·1) (0·1>p>0·05).

Platelet aggregation, expressed as the percentage fall in platelet count was significantly greater in the diabetic children when compared with normal children at 2 minutes (p<0·01). Significant differences were also observed at 1, 3, and 4 minutes but not at 8 minutes after stirring (table 2). The 2 minute value was used for subsequent analysis.

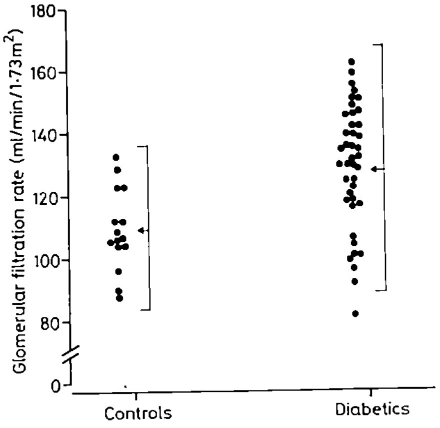

Fig 2 *Geometric mean and range (2 SD) for glomerular filtration rate in ml/min/1·73 m$^2$ surface area for diabetic children and controls.*

Table 2 *Platelet aggregation expressed as percentage fall in platelet count in stirred whole blood in the diabetic children compared with normal children*

| *Time (minutes)* | *Diabetic children Mean (SEM)* | *Normal children Mean (SEM)* | *p Value (t test)* |
|---|---|---|---|
| 1 | 10·4 (0·9) | 6·1 (1·0) | <0·05 |
| 2 | 17·8 (1·2) | 12·3 (1·5) | <0·01 |
| 3 | 27·5 (1·4) | 22·2 (2·1) | <0·01 |
| 4 | 36·5 (1·5) | 31·4 (2·2) | <0·01 |
| 8 | 49·0 (1·4) | 45·0 (2·5) | <0·5 |

### INTER-RELATIONSHIPS

UA/UC correlated with age (r=0·35, p<0·005) in the diabetic but not in the normal children (r=0·14). The association in the diabetic children was not attributed to disease duration, as this did not correlate significantly with UA/UC (r=0·08). Of the diabetic children who had UA/UC above the normal range, five were prepubertal or in early puberty and 10 were in late puberty ($\chi^2$=3·2, 0·05>p>0·1). In the normal children, the geometric mean (range) UA/UC was similar in those in Tanner pubertal stages 1, 2, and 3, 0·41 (0·2–1·0), to those in pubertal stages 4 and 5, 0·41 (0·3–1·3). There was no significant relationship between UA/UC and age at onset of diabetes.

UA/UC correlated weakly with HbA$_{1c}$ (r=0·36, p<0·01). As both UA/UC and HbA$_{1c}$ correlated with age, multiple regression was performed to hold this confounding variable constant. The association between UA/UC and HbA$_{1c}$ was still significant (p<0·05). There were no significant associations between $HbA_{1c}$ and the other parameters measured.

Examining the association between UA/UC and glomerular filtration rate it was observed that, although there was no significant linear correlation ($r=0{\cdot}29$, $p<0{\cdot}07$), seven of the 10 diabetic children who had UA/UC above the normal range also had glomerular filtration rate above the normal range (fig 3) ($p<0{\cdot}001$, $\chi^2$).

There was a significant correlation between UA/UC and renal size ($r=0{\cdot}45$, $p<0{\cdot}001$) and although mean renal size in the diabetic children was not significantly increased, those with UA/UC above normal more often had kidneys above normal mean length for height ($p<0{\cdot}002$, $\chi^2$) (fig 4). The correlation between UA/UC and renal size was still significant ($r=0{\cdot}45$) if only those children in whom glomerular filtration rate had been measured were included ($n=41$). There was also a significant correlation between glomerular filtration rate and renal size ($r=0{\cdot}56$, $p<0{\cdot}001$) (fig 5).

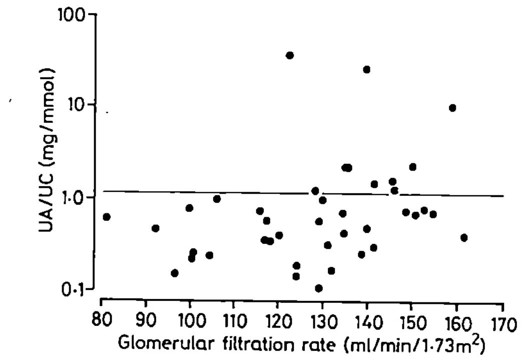

Fig 3 *Association between UA/UC in mg/mmol (log scale) and glomerular filtration rate in 41 diabetic children. The upper 95% tolerance limit for UA/UC in the controls is indicated.*

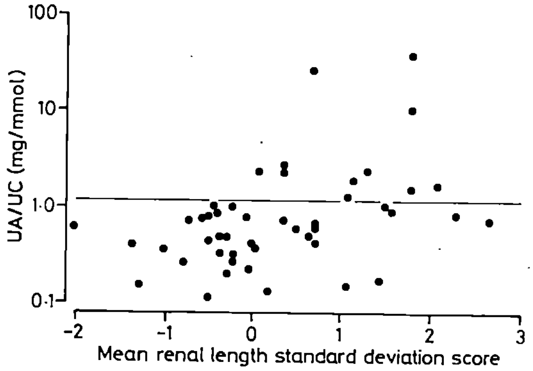

Fig 4 *Association between UA/UC in mg/mmol (log scale) and renal size standard deviation score. The upper 95% tolerance limit for UA/UC for the controls is indicated.*

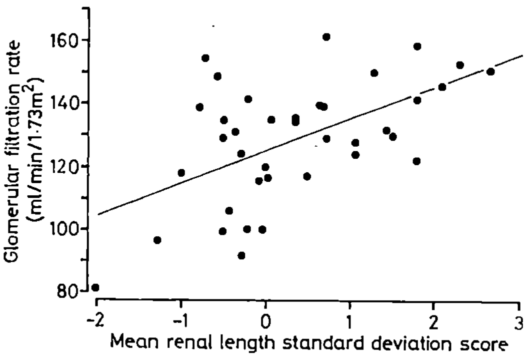

Fig 5 *Association between glomerular filtration rate and renal length for height standard deviation score.*

Neither systolic nor diastolic blood pressure correlated significantly with any of the above markers.

There was no significant association between platelet aggregation and any of the parameters of renal function measured. However, there was a significant correlation with disease duration ($r=0{\cdot}35$, $p<0{\cdot}01$). Eight of the 25 (32%) children who had had diabetes for more than seven years (the mean disease duration for the group) had platelet aggregation at 2 minutes above the normal range, whereas no child who had had the disease for less than seven years had abnormal platelet aggregation ($p<0{\cdot}01$, $\chi^2$). If age, which correlated with disease duration, is held constant using multiple regression analysis, the association between platelet aggregation and disease duration remains significant ($p<0{\cdot}01$). Furthermore, there was no significant correlation between platelet aggregation in the controls.

## Discussion

The prevalence of high UA/UC observed in the diabetic children in this study was similar to that in previous studies.[11-14] UA/UC increased with age and progression through puberty and was not correlated with disease duration. Rowe *et al* also observed an association between UA/UC and age, after controlling for disease duration.[12] In both his study and that of Mathiesen *et al*,[11] raised urinary excretion of albumin was more prevalent in children over the age of 14 or 15. At variance with our results, Davies *et al* reported a small effect of age on the urinary albumin excretion rate but not UA/UC in normal children.[13] Although he observed no significant association between urinary albumin excretion rate and age in diabetic children, however, those with a urinary albumin excretion rate above the normal range were significantly older than those with a normal rate.[13] These studies have used urinary albumin excretion rate to express results of albumin excretion whereas results were expressed as UA/UC in this study. In 47 of the 60 diabetic children where accurate timed urine collections had been made, however, urinary albumin excretion rate values were also available and in these children an association between the rate and age was also found ($r=0{\cdot}33$, $p<0{\cdot}02$).

Rowe *et al* suggested that puberty might be an important factor in the development of nephropathy. He divided the children into two groups according to age (less than or more than 12 years), however, and not according to pubertal stage. In our study, 66% of children with increased UA/UC were in late puberty irrespective of duration of diabetes. Although suggestive of an effect of puberty on the level of UA/UC, the effect of age was greater and it is impossible to separate these two confounding variables.

UA/UC tended to increase with an increasing concentration of $HbA_{1c}$ even allowing for the effect of increasing age on $HbA_{1c}$. The degree of correlation between UA/UC and $HbA_{1c}$ observed in this study was similar to that reported by Rowe *et al*[12] and by Davies *et al*,[13] but this is in contrast with other studies where no associations between urinary albumin excretion and degree of metabolic control were observed.[14 37]

We found that 39% of diabetic children had a raised glomerular filtration rate compared with normal controls. The glomerular filtration rate values in this study were very similar to previous reports,[13–16] although we have found that the clearance of $^{51}Cr$ edetic acid gives estimates of glomerular filtration rate which are about 6% lower than that of inulin.[38] Although adult control subjects were used in this study, their mean glomerular filtration rate was very similar to that of Berg and Thalme; using an inulin clearance technique, they observed a mean value of 114 ml/min/1·73 $m^2$ in group of 13 normal children and adults.[15]

There was no association observed between glomerular filtration rate and age or disease duration in this study. This is in accordance with both Dalquist *et al* who observed no difference in glomerular filtration rate between children with disease duration of less than five, five to 10, or more than 10 years,[14] and Davies *et al* who observed no correlation between either age or disease duration.[13] Berg and Thalme observed an increase in glomerular filtration rate up to a five year disease duration and an inverse relationship thereafter, despite the absence of albuminuria. However, this was assessed by Albustix and not by more sensitive techniques.[1]

When examining the association between UA/UC and glomerular filtration rate, significance was found with a $\chi^2$ test but not with linear regression, which suggests a threshold effect rather than a linear relationship. This is in contrast to the findings of Davies *et al* who observed no difference in glomerular filtration rate between those with normal and those with increased urinary excretion of albumin,[13] and there have been few other studies of these two parameters in diabetic children. Of the three children with raised UA/UC but glomerular filtration rate in the normal range, one had persistent microalbuminuria and marginally raised blood pressure. Her glomerular filtration rate may have been declining with increasing UA/UC.[4] Most of the children with raised UA/UC had values above normal but below the 'microalbuminuric' range, however, the consensus for which is >20 μg/min/1·73 $m^2$, and which has been shown to predict nephropathy.[3–7] We have reported the association between UA/UC and urine albumin excretion rate in normal and diabetic children.[8] The 95th centile for UA/UC in the normal children on two overnight urines was equivalent to an albumin excretion rate on two overnight urines of 8·2 μg/min/1·73 $m^2$, very similar to that reported by Davies *et al.*[39] In this study, UA/UC above this level was associated with abnormally high glomerular filtration rate and larger than average kidney size.

We found no significant increase in renal size in diabetic children compared with a population of normal children. These findings are surprising, and contrast with previous reports of increased kidney size in adults with IDDM.[17–19] We did, however, find a significant correlation between glomerular filtration rate and kidney size as has been reported previously in both normal and diabetic individuals,[19] and our data also showed an association between UA/UC and renal size.

Hypertension is known to increase the rate of deterioration in renal function in diabetic nephropathy. Although some studies have shown minor increases in blood pressure in diabetic children,[22] most studies of diabetic children without microalbuminuria have found them to be normotensive.[23] In this study, we found no significant differences in systolic blood pressure standard deviation score but did find an increase in diastolic blood pressure standard deviation socre compared with normal children from the 1987 American Task Force Data.[26] These results are in agreement with Davies *et al*, who used the French normal data from which to calculate standard deviation scores.[13] A criticism of the Task Force Data has been that blood pressure during childhood may relate better to height than to age.[24] In our study, however, we related the raw blood pressure data not only to age, but also to height, weight, and surface area using a multiple regression model. We found that blood pressure related best to age (data not shown), possibly because half of these diabetic children were in late adolescence and therefore more comparable with an adult population. Contrary to some[11 30] but not other[13] studies, we observed no correlation between blood pressure and either UA/UC or glomerular filtration rate.

We found an increase in platelet aggregation in stirred whole blood in this group of diabetic children compared with normal children. The role of platelets in the pathogenesis of diabetic nephropathy is unclear. Abnormal platelet function has been reported in other renal diseases including glomerulosclerosis[40] and platelet activation results in the release of cationic substances including platelet factor 4 (PF4) and mitogens such as platelet derived growth factor. Both could be involved in the pathogenesis of diabetic nephropathy, PF4 by binding to glomerular polyanions thereby increasing the permeability of glomerular capillaries to anionic albumin and platelet derived growth factor by causing mesangial cell proliferation.[41] Despite these theoretical reasons for linking abnormal platelet aggregation to the early increase in urine albumin excretion seen in these young diabetics, however, we were unable to show any association in this cross sectional study. In addition, the association found between platelet aggregation and disease duration would tend to support the argument that abnormalities in platelet function are secondary to microvascular damage rather than integral to any pathogenetic mechanisms in the development of nephropathy.

Combining these observations on early markers of renal function in children and adolescents with IDDM, we conclude that urinary albumin excretion that is above normal but not necessarily in the predictive microalbuminuric range for the development of nephropathy, is associated with a higher glomerular filtration rate and larger than average kidney size, but there is no association with blood pressure. Longitudinal follow up of these early markers is required to study their variability and to delineate their possible pathogenetic and predictive roles in the development of nephropathy in IDDM.

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# Association between diabetes, severe hypoglycaemia, and electroencephalographic abnormalities

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SUMMARY Serial electroencephalographic recordings were made in 70 diabetic children and findings were related to age at electroencephalography and at diagnosis, duration of diabetes, daily insulin dose, long term metabolic control assessed by glycated haemoglobin $A_1$ ($HbA_1$) concentrations, and severe hypoglycaemic episodes. Abnormalities were found in 18 (26%) of diabetic children, and in only five (7%) of control subjects. There were no associations between electroencephalographic abnormalities and duration of diabetes, daily insulin dose, or $HbA_1$ concentration. Diabetic children with electroencephalographic abnormalities were younger, had an earlier onset of diabetes and 21/34 (62%) of them had previously severe attacks of hypoglycaemia, whereas abnormalities were found in only 13/43 (30%) of diabetic children who had not had severe hypoglycaemia. All diabetic children with hypoglycaemic convulsions had permanent electroencephalographic abnormalities. The degree of metabolic control had no effect on the electroencephalographic findings during the early years of diabetes, but previous severe hypoglycaemia, young age, and early onset seem to be important risk factors for electroencephalographic abnormalities.

Prolonged and recurrent hypoglycaemia can cause permanent brain damage[1] and the brains of infants and children appear to have an increased vulnerability to hypoglycaemia.[2] Hypoglycaemia induced by exogenous insulin injection in diabetes mellitus is the commonest form of hypoglycaemia in children. It is important therefore, to assess the possible effect of hypoglycaemia on the brain of diabetic children. Furthermore other metabolic abnormalities of diabetes—for example, chronic hyperglycaemia and ketosis—could also have a harmful effect on the central nervous system.

Several studies of electroencephalograms in diabetic children have been published,[3-8] which tried to find an association between electroencephalographic features and hypoglycaemia, as well as to correlate these abnormalities with diabetic control and microvascular complications among other things. Almost all of these observations were reported 15 to 20 years ago, however, and only scarce reports are available for the last decade during which important changes have taken place in the management of diabetic children—for example, the introduction of new insulins and insulin delivery devices, and better methods for assessment of metabolic control.

At least two of these developments make it necessary to look again at the electrophysiological abnormalities in diabetic children. Firstly, with regular measurements of stable glycated haemoglobin $A_1$ ($HbA_1$) concentrations it is now possible to assess objectively the degree of long term metabolic control and relate it to the electroencephalographic changes. Secondly, the introduction of new methods of intensified insulin treatment is likely to increase the incidence of hypoglycaemia, and the risk of hypoglycaemic brain damage may also increase. For the future assessment of this possibly increasing risk, therefore, it is essential to have information on the frequency of severe hypoglycaemic attacks as well as on the extent of hypoglycaemia related electroencephalographic abnormalities under the present diabetic management before increasing the use and availability of intensive insulin treatment.

The aim of this study was to analyse the influence of various factors on the electroencephalographic pattern in diabetic children with particular reference to long term metabolic control and previous attacks of severe hypoglycaemia.

## Patients and methods

Seventy diabetic children, 37 girls and 33 boys, mean (SEM) age 11·2 (0·5) years, and duration of diabetes 5·0 (0·4) years, participated in the study. None of them had any perinatal diseases, a personal or family history of epilepsy, or neurological symptoms. All children were followed up in our diabetic clinic using the same principles of insulin and dietary treatment, which included twice daily injections of short and intermediate acting insulin and restricted carbohydrate diet. Metabolic control was assessed by regular (three to five times a year) measurements of $HbA_1$ concentrations. None of the children had albuminuria, retinopathy, or arthropathy.

The case notes of all children were carefully studied retrospectively, and every severe hypoglycaemic episode was recorded (defined as loss of consciousness or convulsions, or both, requiring the assistance of a second person). The retrospective diagnosis of hypoglycaemia was based on the clinical symptoms and on the effect of parenteral glucagon. Blood glucose was measured in only five cases (mean 1·9 mmol/l). Mild and moderate hypoglycaemic episodes occurred in all children with variable frequency. As neither the parents nor the children were able to give a reliable record of these events the episodes were not evaluated.

At the time of the study, the children were in good general condition with blood glucose concentrations between 6 and 14 mmol/l. Electroencephalographic recordings were carried out with an eight channel electroencephalograph using the 10–20 international system. Recording at rest (usually in the afternoon) lasted for at least 20 minutes including hyperventilation. In children with previous hypoglycaemic episode(s), the electroencephalogram was recorded at least one month after the hypoglycaemic episode (mean (SEM) 25 (5), range 2–96 months). If an abnormality was found, the recording was repeated after a mean period of 15 (2) months. The electroencephalogram of age matched (mean age 10·9 (0·41) years) normal controls (37 girls and 33 boys) were also assessed by the same investigator without knowledge of their clinical state. The electroencephalogram was analysed visually by one of us (GA) who had no information of the children's clinical and laboratory data. Recordings were classified according to the following scale taking into account the characteristic age dependent changes as suggested by Haumont *et al*[5] and Tsuboi.[9] *Grade 1:* Normal background activity. *Grade 2:* Borderline disease: irregular basic rhythm with marked excess of slow waves or synchronisation. *Grade 3:* Asymmetry on background activity, small sharp waves or moderate to severe 'slow down' effects of hyperventilation. *Grade 4:* Paroxysmal pattern: spike waves. *Grade 5:* Paroxysmal pattern: spike groups.

For the statistical analysis of the data Student's *t* test and the $\chi^2$ test were used.

## Results

Abnormal electroencephalogram patterns (grades 2 to 5) were found in 34 (49%) of the diabetic children compared with 17 (24%) of the controls ($p<0·05$). If only grade 3 to 5 abnormalities were considered, 18 children (26%) had abnormal electroencephalograms, still a high figure considering that these abnormalities were found in only five (7%) of the 70 normal, healthy children ($p<0·01$). Table 1 shows that, in contrast to the controls, diabetic children with abnormal electroencephalogram were significantly younger ($p<0·01$). Diabetic children with electroencephalogram abnormalities also had earlier onset of diabetes. There was, however, no significant difference between those with normal and abnormal electroencephalograms in the duration of diabetes, mean daily insulin dose, or mean $HbA_1$ concentrations (mean of the last five years).

The incidence of electroencephalographic abnormalities, however, was significantly higher in those

Table 1 *The association between abnormal electroencephalogram and age, duration of diabetes, daily insulin dose, and $HbA_1$ concentration. Values are expressed as mean (SEM)*

| | *Age at electroencephalogram (years)* | | *Age at diagnosis (years)* | *Duration of diabetes (years)* | *Daily insulin dose (U/kg)* | *$HbA_1$ concentration (%)* |
|---|---|---|---|---|---|---|
| | *Control subjects* | *Diabetics* | | | | |
| Normal electroencephalogram | 10·3 (1·7)<br>(n=53) | 12·8 (0·7)<br>(n=36) | 7·6 (0·6) | 5·8 (0·6) | 0·97 (0·05) | 11·3 (0·2) |
| Abnormal electroencephalogram | 10·5 (2·8)<br>(n=17) | 9·6 (0·7)<br>(n=34) | 4·8 (0·6) | 4·5 (0·6) | 0·85 (0·07) | 11·4 (0·2) |
| p Value | >0·5 | <0·01 | <0·01 | 0·1 | 0·1 | >0·5 |

children who had a history of one or more severe hypoglycaemic episodes compared with those who had no such episodes (table 2) ($p<0\cdot001$). Almost 80% of the children with previous severe hypoglycaemia had abnormal electroencephalograms, whereas abnormalities could be detected in only 30% of the non-hypoglycaemic group (table 2). In other words, only 22% hypoglycaemic children had normal electroencephalograms as opposed to 77% of those without previous severe hypoglycaemia ($p<0\cdot001$). Table 2 also shows that only six out of 36 children (17%) with normal electroencephalograms had severe hypoglycaemia, whereas 21 out of 34 children (62%) with abnormal electroencephalograms had hypoglycaemic episode(s) ($p<0\cdot001$).

The grading of abnormalities (table 3) shows even more clearly the effect of hypoglycaemia. Fourteen out of the 21 hypoglycaemic children with abnormal electroencephalograms (67%) had grade 3 to 5 abnormalities, whereas most non-hypoglycaemic diabetics in this 'abnormal electroencephalogram' group had only borderline abnormalities (grade 2) and none had grade 4 to 5 abnormalities. If only grade 3 to 5 findings are considered, our data show a fivefold increase in the incidence of electroencephalographic abnormalities in the hypoglycaemic group (14 out of 27 children) compared with the non-hypoglycaemic group (four out of 43 children). In comparison, no control children had grade 5 abnormalities, and only one had a grade 4 abnormality. The finding that all the 11 children who had hypoglycaemic convulsions had abnormal electroencephalograms further emphasises the association between hypoglycaemia and electroencephalographic abnormalities.

Table 2 *The association between electroencephalographic abnormalities and previous hypoglycaemia*

| | *No with hypoglycaemic episodes* | *No without hypoglycaemia* |
|---|---|---|
| Normal electroencephalogram | 6 | 30 |
| Abnormal electroencephalogram | 21 | 13 |

$\chi^2=14\cdot75$, $p<0\cdot001$.

Table 3 *Electroencephalographic abnormalities in diabetic children*

| *Abnormal electroencephalogram* | *No with hypoglycaemic episodes* | *No without hypoglycaemic* |
|---|---|---|
| Grade 2 | 7 | 9 |
| Grade 3 | 9 | 4 |
| Grade 4 | 3 | 0 |
| Grade 5 | 2 | 0 |
| Total | 21 | 13 |

Eight of the 27 children in the hypoglycaemic group had two or more severe episodes. Altogether 37 severe hypoglycaemic episodes occurred in the 27 children, which gives an incidence rate of 0·28 episodes/patient year for the 'hypoglycaemic group' and a rate of 0·12 episodes/patient year for the whole group. It is interesting to note that the electroencephalogram was negative in only one of the eight children with repeated severe attacks of hypoglycaemia.

In 21 of the 27 children with hypoglycaemia, recordings were repeated after a mean period of 15 (2) months. The same degree of abnormality was found in 15 cases, the electroencephalogram remained normal in four cases, and a previously unrecorded abnormality developed in two cases.

Finally, in an attempt to identify risk factors for hypoglycaemia, table 4 shows that the mean age at diagnosis, duration of diabetes, daily insulin dose, and HbA$_1$ concentrations were not significantly different in the hypoglycaemic and non-hypoglycaemic groups, but hypoglycaemic children were significantly younger.

Table 4 *Clinical data of diabetic children with and without hypoglycaemic episodes. Values are expressed as mean (SEM)*

| | *Age at electro-encephalography (years)* | *Age at diagnosis (years)* | *Duration of diabetes (years)* | *Daily insulin dose (U/kg)* | *HbA$_1$ concentration (%)* |
|---|---|---|---|---|---|
| Diabetics with severe hypoglycaemia | 9·7 (0·8) | 5·0 (0·7) | 4·9 (0·6) | 0·9 (0·1) | 11·3 (0·2) |
| Diabetics without severe hypoglycaemia | 12·3 (0·7) | 7·2 (0·6) | 5·1 (0·5) | 0·9 (0·1) | 11·4 (0·2) |
| p Value | <0·02 | >0·5 | >0·5 | >0·5 | >0·5 |

## Discussion

The results of the present study confirm previous data showing that diabetic children have an increased incidence of electroencephalographic abnormalities compared with the general population.[3–8] Our incidence is in the range reported by others,[3–6] but comparison is difficult due to the different electroencephalographic criteria used by different authors. As our results have shown, the incidence was high (49%) when all abnormalities including 'borderline' changes were considered, but was considerably lower (26%) if only grade 3 to 5 abnormalities were regarded as abnormal.

The aetiology and pathogenesis of these abnormalities is not entirely clear. Several studies have tried to analyse the role of metabolic control, microvascular and other late complications, and previous hypoglycaemia. Some earlier[3–4] and some more recent[5 8] studies suggested a positive correlation between electroencephalographic abnormalities and the degree of metabolic control. The criteria for metabolic control in these reports, however, were somewhat arbitrary; the terms 'good', 'moderate', 'insufficient', and 'poor' were used and the grouping of diabetic children according to these criteria was based on unreliable record books, sporadic measurements of glycosuria, ketonuria, and blood glucose concentrations. Only the advent of $HbA_1$ measurements has given us the possibility for the objective long term assessment of metabolic control, and our study is the first to report on the association between metabolic control (measured by $HbA_1$) and electroencephalographic abnormalities. We found no correlation between electroencephalographic abnormalities and metabolic control or duration of diabetes. This finding suggests that chronic hyperglycaemia alone is probably not a major factor in causing these abnormalities, although there was not a wide variation of the $HbA_1$ values and diabetes was of comparatively short duration in the diabetic children studied.

Our results clearly show that electroencephalographic abnormalities were associated with the frequency of previous severe attacks of hypoglycaemia.[3 5 7] The vast majority (80%) of children with severe hypoglycaemia had some degree of electroencephalographic abnormalities, only one of eight children with repeated severe hypoglycaemia had a normal electroencephalogram, and every child with hypoglycaemic convulsions had some abnormality (n=11). These findings, however, do not prove a causal relationship between hypoglycaemia and electroencephalographic abnormalities. As electroencephalographic recordings were not made at the time of diagnosis of the diabetes, it is possible that some of the diabetic children had pre-existing electroencephalographic abnormalities and these children were more likely to have a seizure during an episode of hypoglycaemia. The electroencephalographic abnormalities in hypoglycaemic children seems to be permanent lesions still detectable after a mean observation period of 15 months.

Because severe hypoglycaemia seems to be associated with electroencephalographic abnormalities in diabetic children, we have also estimated its incidence in our diabetic population. The overall incidence of severe hypoglycaemia in our cohort of patients was 0·12 episodes/patient year, which is in accordance with recently published data on conventionally treated diabetic patients.[10] With the knowledge on the incidence of severe hypoglycaemia and electroencephalographic patterns, one may hypothesise on the influence of hypoglycaemia on the electroencephalogram. Even with the modest incidence of 0·12 hypoglycaemic episodes/year, a diabetic child is likely to have between five and eight severe episodes in his or her lifetime. The cumulative effects of these may well be not negligible.

Finally, we have tried to identify 'hypoglycaemia risk factors', and have shown that hypoglycaemia was not related to daily insulin dose, age at diagnosis, or duration of diabetes, but the mean age of the 'hypoglycaemic group' was significantly lower.

Although hypoglycaemia seems to be the major factor associated with electroencephalographic abnormalities there must have been other risk factors as well, as the incidence of abnormalities in the 'non-hypoglycaemic' group was also higher than in the general population. These possible risk factors cannot be identified in our study. It is possible that some children already had subclinical microvascular lesions or that there is indeed a 'primary diabetic encephalopathy' as suggested by Eeg-Olofson and Petersen.[3]

The clinical relevance of these abnormalities is not known. As we mentioned earlier, none of the children studied had neurological symptoms or neurological abnormalities. In spite of that, serial electroencephalographic recordings seem to be warranted in diabetic children with previous severe hypoglycaemic episodes. Finally, young diabetic children with documented electroencephalographic abnormalities are possibly at an increased risk of brain injury during recurrent hypoglycaemic states, and further studies are needed to clarify whether electroencephalographic recording could be a useful way of selecting patients for intensified insulin treatment to prevent the deleterious effects of hypoglycaemia.

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# Do education groups help diabetics and their parents?

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SUMMARY The importance of education in the management of diabetes is recognised but has rarely been assessed in children. In a longitudinal controlled study we have examined the effect of a programme of education on the knowledge, diet, and concentration of glycated haemoglobin $A_{1c}$ in a group of diabetics. The programme took the form of two packages of education each consisting of four weekly meetings, in which small groups of parents and older children were led in a discussion of different aspects of diabetes. Only one of the 119 families who began the study failed to complete it. Family knowledge about diabetes improved as a result of the programme, although this was poorly retained in the fathers. A trend to improvement in several aspects of diet was noted but did not reach significance. A significant fall in glycated haemoglobin $A_{1c}$ was apparent seven months after the education in children aged 11 years and over. Those whose initial control was poor improved most. We conclude that such meetings should be considered as a useful adjunct to regular diabetic clinics.

There are three aims of the treatment of a child with diabetes: normal metabolism (in the belief that this will reduce short and long term morbidity),[1] satisfactory growth, and as normal a lifestyle as is possible for the patient and family. Achieving these aims, however, is a complex process that makes great demands on a family and so there are many stages at which management may be less than perfect.

In 1985 an audit of all children with diabetes at five clinics on Tyneside and Teeside was undertaken to determine which aspects of management could be improved. Knowledge about diabetes and practical skills were found to be very variable and diet too was less than optimal.[2] [3] Of the factors measured that independently correlated with the child's glycated haemoglobin $A_{1c}$, only the family's knowledge about diabetes was apparently amenable to change. More diabetic children than controls were perceived by their parents to have behavioural problems. This was less apparent in those with better knowledge about diabetes.[4] These findings suggested the need for a method of improving knowledge about diabetes that would not generate anxiety.

There have been several studies of the effects of educational programmes on the care of diabetics and most of these have found some benefits, at least in the short term.[5–8] There have been few large scale studies of children, however, the effect of reinforcing a basic programme of education has not been assessed, the follow up has often been either erratic or short term, and some educational inputs have been complex and costly. This study was designed to create and evaluate a structured programme of education that could be run with limited resources at any clinic. It was based upon meetings at which the professionals enabled small groups of families to share their knowledge and experience of diabetes.

## Patients and methods

Patients attending children's diabetic clinics in Newcastle, Gateshead, North Tees, and Middlesbrough were invited to take part. Most had previously taken part in the audit study and some who had transferred to adult clinics were still included. The volunteers were stratified according to the child's age, sex, and diabetic control (concentration of glycated haemoglobin $A_{1c}$) and the most recent occupation of the father (socioeconomic group). They were then randomly allocated to one of four experimental cohorts that were balanced for these variables. Each cohort was subdivided into four, taking into account the addresses of the families, to give groups of manageable size (six to 10 families) for the educational programme.

All families were assessed at the beginning of the study and those in cohorts 1 and 2 were invited to the primary educational package. All families were reassessed eight months later and then those in cohort 1 were invited to a second, reinforcement, educational package and those in cohort 3 to the primary package for the first time. All families were assessed again at the end of the study, 16 months after the start, after which those in cohort 4, the controls, were invited to the primary educational package (table 1). The study began in May 1985 when one group from cohort 1 or 2 and one from cohort 3 or 4 were assessed. Two more groups were assessed each calendar month thereafter, the final assessments being in July 1987. Throughout the study all the intervals between assessments were constant.

Each assessment was similar and consisted of a home visit by AFH at which standard social information was obtained, and a capillary blood sample taken, using the Unistep procedure (Ciba Corning), for the estimation of glycated haemoglobin $A_{1c}$ concentrations. All the blood samples were analysed in one laboratory by gel electrophoresis after removal of the labile fraction.[9] The normal range for adults by this method is 5·0–7·5%. Knowledge was assessed using one of five multiple choice questionnaires designed for this study,[10] which was chosen at random and given to children aged 11 years and older and their parents. A dietary diary for the three days before the visit was completed by either parent or child. This record of what the child ate was checked and quantified at the home visit.[3] The fat and carbohydrate intakes were expressed as the proportion of total energy, and fibre intake was also calculated in relation to energy intake. Those families scheduled for invitation to meetings were given a printed timetable and were encouraged to attend. At the routine clinic appointment closest to each assessment a random blood sample was requested for estimation of C peptide concentration from every child unless already known to be C peptide negative (<0·18 nmol/l).

The content of the educational packages has been described elsewhere.[11] Each package consisted of four, one and a half hour, discussions facilitated by two members of the research team and had a printed worksheet to maintain consistency. The four meetings in the primary package covered background and management, insulin, diet, and practical problems. The four reinforcement meetings were designed to complement and to follow the primary package and consisted of a quiz, tests of skill, problem solving discussion groups, and a showing of the video 'The way of life' sponsored by Nordisk – UK. An individual who was present for at least two sessions of a series was deemed to have attended the meetings and the family 'attended' if any family member met this criterion. There was an extra assessment of knowledge by a further multiple choice questionnaire at the end of the final meeting in each series.

The data were analysed separately for families with children aged under and over 11 years because only the older children completed the multiple choice questionnaires and were encouraged to attend the meetings. Furthermore, from the age of 11 years most children would be expected to be making a considerable independent contribution to the management of their diabetes.

The results of the multiple choice questionnaires were analysed separately for mothers, fathers, and children. A linear model,[12] which eliminated the between person variation, was used to test whether there was any difference between the baseline score for an individual and the scores achieved (a) immediately after education, (b) after a lag of seven months, and (c) after a lag of 15 months (with no intervening education). The tests for these results were done hierarchically as there was no basis for thinking that there may have been an effect at 15 months with no corresponding effect at seven months. The model also allowed a check to be made for the presence of systematic effects upon questionnaire scores from any other cause; none was found.

The dietary and glycated haemoglobin $A_{1c}$ results were analysed by analysis of covariance. The covariates considered were the initial level of the variable being investigated, socioeconomic group, age, sex,

Table 1 *Overall study design*

| | *No of families (n=119)* | *Month* | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* |
| Cohort 1 | 32 | A1 | E1 | | | | | | | A2 | E2 | | | | | | | A3 | |
| 2 | 29 | A1 | E1 | | | | | | | A2 | | | | | | | | A3 | |
| 3 | 32 | A1 | | | | | | | | A2 | E1 | | | | | | | A3 | |
| 4 | 26 | A1 | | | | | | | | A2 | | | | | | | | A3 | E1 |

A1=initial assessment, A2=second assessment, A3=final assessment, E1=primary educational package, E2=reinforcement package.

and duration of the diabetes. Only the initial level of the variable under investigation was found to be important.

## Results

One hundred and nineteen families, 46% of those invited, agreed to take part in the study and completed the first assessment. The second and third assessments were completed by 118 families, although dietary data were not available for two families at the third assessment. This was because of marital problems in one family and extensive hospitalisation of the child in the other. The only family not to complete the study moved from the area. These families with incomplete data were all in different cohorts. There were no significant differences between the children in the different cohorts at the initial assessment apart from a greater proportion of subjects in socioeconomic groups 1 and 2 in cohort 4 (table 2). This was caused by the loss of a small number of families after stratification but before the first assessment.

### ATTENDANCE

The primary package (E1) was attended by 68% of

Table 2 *Details of children with diabetes in the cohorts at the initial assessment. Results are number or mean (SD)*

| | *Cohorts* | | | | |
|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *Total* |
| Sex (boys/girls) | 20/12 | 19/10 | 17/15 | 18/8 | 74/45 |
| Socioeconomic group | | | | | |
| 1+2 | 15 | 9 | 14 | 15 | 53 |
| 3+4 | 13 | 13 | 14 | 7 | 47 |
| 5+6 | 3 | 5 | 4 | 3 | 15 |
| 7+8+9 | 1 | 0 | 0 | 0 | 1 |
| Age (years) | 12·7 (2·9) | 11·4 (3·3) | 12·4 (3·6) | 11·7 (3·3) | 12·1 (3·3) |
| Glycated haemoglobin $A_{1c}$ (%) | 11·1 (2·7) | 11·2 (1·7) | 11·0 (2·3) | 10·8 (2·1) | 11·1 (2·2) |
| C peptide | | | | | |
| ≤0·18 nmol/l | 27 | 25 | 31 | 23 | 106 |
| <0·18 nmol/l | 1 | 1 | 0 | 1 | 3 |
| Duration of diabetes (years) | 4·6 (2·9) | 5·9 (2·8) | 5·3 (3·2) | 5·0 (3·1) | 5·2 (3·0) |

Table 3 *Scores on multiple choice questionnaire of families who attended the meetings to which they were invited (cohorts 1–3), of those not invited (cohort 4), and of those who although invited did not attend. Results are mean (number of questionnaires completed)*

| *Score at:* | *Initial assessment (A1)* | *After education (E1)* | *Second assessment (A2)* | *After education (E1 or E2)** | *Final assessment (A3)* | *After education (E1)* |
|---|---|---|---|---|---|---|
| **Mothers:** | | | | | | |
| Cohort 1: | 18 (24) | 21 (22) | 19 (24) | 21 (23)* | 20 (23) | |
| 2: | 15 (19) | 21 (18) | 20 (19) | 19 (14) | 18 (19) | |
| 3: | 16 (14) | | 15 (14) | | 17 (13) | |
| 4: | 19 (25) | | 20 (25) | | 20 (25) | 23 (20) |
| Did not attend: | 15 (32) | | 15 (30) | | 16 (32) | |
| **Fathers:** | | | | | | |
| Cohort 1: | 17 (23) | 20 (21) | 16 (23) | 19 (21)* | 17 (22) | |
| 2: | 12 (14) | 19 (13) | 12 (13) | 19 (12) | 15 (12) | |
| 3: | 15 (13) | | 16 (13) | | 17 (13) | |
| 4: | 15 (24) | | 17 (22) | | 17 (23) | 20 (19) |
| Did not attend: | 14 (29) | | 14 (29) | | 14 (27) | |
| **Children with diabetes:** | | | | | | |
| Cohort 1: | 11 (18) | 15 (18) | 15 (19) | 17 (20)* | 16 (19) | |
| 2: | 10 (12) | 14 (9) | 13 (12) | | 12 (12) | |
| 3: | 11 (8) | | 12 (8) | 15 (8) | 13 (9) | |
| 4: | 10 (20) | | 11 (19) | | 12 (20) | 17 (17) |
| Did not attend: | 10 (23) | | 10 (24) | | 14 (27) | |

*Score after reinforcement.
A typical between subject standard deviation was 5·5.

those families invited and the reinforcement (E2) by 77%. Attendance was not related to the age or sex of the child, glycated haemoglobin $A_{1c}$ concentration, socioeconomic group, or duration of the diabetes. British Diabetic Association (BDA) members, however, were more likely to attend (48 families of the 64 BDA members attended compared with 15 of the 29 non-members invited).[11]

### SCORES ON MULTIPLE CHOICE QUESTIONNAIRE

Table 3 shows the mean scores on the multiple choice questionnaire of the mothers, fathers, and children in families that attended the meetings (cohorts 1–3), of those who were not invited to meetings (cohort 4), and of those invited but who did not attend. The analysis of these data showed strong evidence that the educational package increased the mean questionnaire scores of the mothers, fathers, and children ($p<0\cdot001$ in all cases) in the short term. For the mothers and children there was also strong evidence that the mean questionnaire scores were still raised seven months after the education ($p<0\cdot001$ in both cases); there was no evidence of this for the fathers ($p>0\cdot05$). There was a suggestion that the mean questionnaire scores of the mothers and children were increased at 15 months after the education ($p<0\cdot10$), but as this effect can only be assessed for cohort 2 ($n=29$), the test has low power. The mean increases in questionnaire scores, adjusted for the differences between individuals, with 95% confidence intervals, are shown in table 4. There was no evidence that the effect on the questionnaire scores of the reinforcement package, preceeded by the primary package, was different from that achieved by the primary education package alone ($p>0\cdot05$).

In general, the scores of the mothers and children changed in a way similar to that which might have been anticipated from the study design; an appreciable rise in the short term followed by a slow decay. The scores of the fathers, however, showed no evidence of sustained improvement. There was no evidence of an effect of socioeconomic group on change in questionnaire scores. Generally, those families who were invited to the meetings but did not attend started and finished the study with the least favourable values.

Table 4 *Adjusted mean increases from baseline in scores on multiple choice questionnaire as a result of being invited to the meetings (95% confidence interval)*

| | *Mothers* | *Fathers* | *Children with diabetes* |
|---|---|---|---|
| Immediate | 3·2 (2·2 to 4·2) | 2·4 (1·1 to 3·7) | 4·9 (3·6 to 6·2) |
| At 7 months | 1·8 (1·7 to 4.2) | −0·3 (−1·5 to 1.0) | 2·9 (1·7 to 4.2) |
| At 15 months | 1·3 (−1·9 to 4·6) | 1·8 (−0·7 to 4·2) | 1·9 (−0·4 to 4·1) |

### DIET

Those children whose families had attended both sets of meetings ended with the lowest fat intakes and the highest intakes of carbohydrate and fibre (table 5). For the children under and over 11 years of age, however, the analysis of covariance indicated that the small changes in diet were not significant. The changes in the dietary components are summarised in table 6.

Table 5 *Dietary intake of children with diabetes whose families attended the meetings to which they were invited (cohorts 1–3), of those not invited (cohort 4), and those who although invited did not attend. Results are means*

| | *No* | *Assessment* | | |
|---|---|---|---|---|
| | | *Initial (A1)* | *Second (A2)* | *Final (A3)* |
| **Fat (%):** | | | | |
| Cohort 1: | 24 | 41 | 38 | 38 |
| 2: | 19 | 41 | 39 | 40 |
| 3: | 14 | 41 | 39 | 41 |
| 4: | 25 | 40 | 39 | 40 |
| Did not attend: | 34 | 41 | 40 | 41 |
| **Carbohydrate (%):** | | | | |
| Cohort 1: | 24 | 45 | 46 | 46 |
| 2: | 19 | 44 | 47 | 46 |
| 3: | 14 | 46 | 46 | 45 |
| 4: | 25 | 45 | 46 | 44 |
| Did not attend: | 34 | 44 | 45 | 43 |
| **Fibre (g/MJ):** | | | | |
| Cohort 1: | 24 | 2·8 | 2·9 | 2·9 |
| 2: | 19 | 2·8 | 2·8 | 2·7 |
| 3: | 14 | 2·6 | 2·6 | 2·6 |
| 4: | 25 | 2·8 | 3·0 | 2·7 |
| Did not attend: | 34 | 2·4 | 2·7 | 2·6 |

Typical between subject standard deviations were: fat 4·5%, carbohydrate 4·5%, and fibre 0·8 g/MJ.

Table 6 *Changes in the dietary intake of children with diabetes whose families attended the meetings to which they were invited (cohorts 1–3), of those not invited (cohort 4), and those who although invited did not attend*

| | *No* | *Mean (SE) carbohydrate (%)* | *Mean (SE) fat (%)* | *Mean (SE) fibre (g/MJ)* |
|---|---|---|---|---|
| Cohort 1: | 24 | 1·6 (0·91) | −2·6 (0·99) | 0·11 (0·148) |
| 2: | 19 | 1·6 (1·11) | −1·2 (1·09) | −0·05 (0·187) |
| 3: | 14 | −1·1 (1·08) | −0·4 (1·12) | 0·03 (0·212) |
| 4: | 25 | −0·8 (0·75) | 0·6 (0·76) | −0·13 (0·181) |
| Did not attend: | 34 | −1·0 (0·90) | 0·2 (0·75) | 0·14 (0·137) |

CONTROL

Like the scores on the multiple choice questionnaire and dietary results, the pattern of changes in glycated haemoglobin $A_{1c}$ concentration was as expected: cohort 1 finished the study with the lowest mean values (table 7). Analysis of covariance showed no effect of the educational package on the glycated haemoglobin $A_{1c}$ concentrations of the children aged under 11 years. For all the children aged 11 years and over, whose families were invited to the meetings, the analysis of covariance indicated that the educational package led to marginal improvements in concentrations of glycated haemoglobin $A_{1c}$. The effect of the education depended upon the initial glycated haemoglobin $A_{1c}$ concentration of the child (test for non-parallelism, F3;72=2·40, p=0·07). For children who initially had glycated haemoglobin $A_{1c}$ concentrations of 8, 12, and 16%, the final concentrations expected for each of the cohorts are given in table 8. Values for the other initial values can be found by linear interpolation.

For those children over 11 years whose families actually attended the meetings the analysis of covariance showed a significant effect of education on glycated haemoglobin $A_{1c}$ concentration (F 3,53=3·58, p=0·02; table 8). The low level of attendance in cohort 3 (only 14 of the 32 families attended) may have introduced some bias into this analysis. The effect of the primary package appeared to be of limited duration as at the end of the study cohort 2 was no better than the controls (cohort 4). The cohorts who had received most recent education, either reinforcement (cohort 1) or the primary package (cohort 3), did best of all.

Table 7 *Glycated haemoglobin $A_{1c}$ concentrations (%) of those children with diabetes whose families attended the meetings (cohorts 1–3), those not invited (cohort 4), and those who although invited did not attend. Results are means*

| | *No* | *Assessment* | | |
|---|---|---|---|---|
| | | *Initial (A1)* | *Second (A2)* | *Final (A3)* |
| Cohort 1: | 24 | 10·9 | 9·5 | 9·9 |
| 2: | 19 | 11·5 | 10·9 | 10·9 |
| 3: | 14 | 10·1 | 11·3 | 10·1 |
| 4: | 25 | 10·9 | 10·9 | 10·4 |
| Did not attend: | 34 | 11·4 | 11·1 | 10·8 |

A typical between subject standard deviation was 2·2%.

Table 8 *Expected final glycated haemoglobin $A_{1c}$ concentration for a selection of initial values. Values are given for children with diabetes aged 11 years and over only: for all families and for those who were invited to the educational packages and did attend*

| | *Initial glycated haemoglobin $A_{1c}$ (%)* | | |
|---|---|---|---|
| | *8·0* | *12·0* | *16·0* |
| **All children, whether families attended or not:** | | | |
| Cohort 1: | 9·0 | 10·5 | 11·9 |
| 2: | 7·7 | 11·3 | 14·9 |
| 3: | 8·8 | 11·2 | 13·8 |
| 4: | 7·8 | 11·2 | 14·5 |
| (The residual standard deviation was 1·7%) | | | |
| **Children whose families attended the meetings:** | | | |
| Cohort 1: | 9·0 | 10·5 | 11·9 |
| 2: | 7·6 | 11·4 | 15·2 |
| 3: | 10·6 | 10·3 | 10·0 |
| 4: | 7·8 | 11·2 | 14·5 |
| (The residual standard deviation was 1·6%) | | | |

## Discussion

This study has shown that a simple educational programme increased the knowledge about diabetes of the mothers, fathers, and children who attended. The improvement in knowledge then decayed (in the fathers very quickly) but an improvement was apparent seven months, and possibly even 15 months, after the programme for mothers and children. The beneficial effects on dietary intake were equivocal but an improvement in concentration of glycated haemoglobin $A_{1c}$ was apparent seven months after the meetings.

The crucial role of education in the management of diabetes is generally recognised.[13] For the past 30 years many studies have shown poor knowledge about diabetes and its management among patients and the parents of diabetic children.[14] Organising groups is a logical way to address this problem. Group meetings prevent needless repetition, reduce barriers between doctor and patient, and help patients to share worries, problems, and experiences. Such programmes, however, make unfamiliar demands upon staff and accommodation; there is no agreed syllabus or generally accepted method, and relatively few suitable teaching aids are available. Furthermore the time which parents, children, and staff can give is limited.

The evaluation of educational programmes is also problematical. Glycated haemoglobin $A_{1c}$ gives an objective measure of mean blood glucose over a lengthy period of time but may conceal unacceptable episodes of hyperglycaemia and hypoglycaemia.[15] A successful programme of education may even lead to a modest rise in glycated haemoglobin $A_{1c}$ concentration in a small number of diabetics from initially over anxious families. Glycated haemoglobin is therefore an imperfect measure of the success of the management of diabetes. Knowledge too cannot be easily assessed; multiple choice questionnaires are usually used but cannot assess practical skills and must be designed and administered with care.[16] In particular, they may not apply equally to families of different backgrounds. Finally, diet is difficult to measure with both reliability and validity.[17] In addition, a change in the proportion of energy from fat or carbohydrate of only 1–2 percentage points nevertheless represents a major change in the eating habits and lifestyle of the child and family. Such changes could only be detected with a very large sample size.

Few programmes of education have been evaluated and the results have been inconsistent.[14] Some have led to improvements in knowledge, control, and diet, and some to no improvements in control despite better knowledge. Several studies, however, have found gains in knowledge and control to be short lived,[6] but all published studies appear to show some benefit for those who took part. Such findings may arise because the association between control and knowledge is complex and mediated by motivation and attitudes and hence compliance.[16] Compliance with even simple therapeutic regimens is often very poor but nobody is completely non-compliant; patients may comply with only some parts of their regimen and these may change with time.[18] For children the situation is even more complex as the parents and others are also involved in the management, and their role changes as the child grows. There is a variety of reasons why changes in control or behaviour may not result from an educational programme even if it does improve knowledge. The demonstration of benefits from a practical programme of education is important and suggests that resources would not be wasted if such a programme were organised as an adjunct to regular clinic visits.

Fathers of diabetic children are less knowledgeable about diabetes than mothers.[9] [14] This, together with the finding that the increase in their knowledge decayed so quickly, even for those who were motivated enough to attend the programme, is cause for concern. It suggests that the role of fathers in day to day management is minimal; this imposes excessive responsibility on mothers and sets a poor example to children. We have previously found that more mothers than fathers had seen their family doctors about their 'nerves'.[4] There is therefore an urgent need for fathers to be encouraged to take a more active role in the management of diabetes.

This educational intervention led to children aged 11 years and over increasing their knowledge about diabetes and improving their control. The improvement in the knowledge of the mothers, however, did not result in better control of the younger children. These findings suggest that priority should be given to educating children.

Our programme required three hours of staff time per session for between six and 10 families; a similar committment of time as a traditional clinic. If the meetings are presented as another facet of the care of diabetics, and incorporated into regular clinics, an excellent response is likely. Evening meetings, however, have the advantage of enabling both parents to attend and a programme to be followed without disrupting schooling. A 'fathers only' meeting may be valuable. In this study the number of meetings chosen and the intervals were arbitrary. Four weekly meetings appeared to be the most that our families would tolerate in one programme but the confidence necessary to allow forthright discussion developed slowly. An important requirement is to allow 'simple human interaction' to occur in a relaxed non-judgmental but refereed setting for which confidence is essential.[19]

As families are expected to take increasing responsibility for the day to day management of diabetes the need for systematic education and revision of practical skills has grown. These are unlikely to be met efficiently by conventional clinic visits, which are necessary for monitoring the health of the child and family and providing individual advice and trouble shooting. We have shown that even a modest programme of group education can result in tangible benefits and recommend that consideration be given to incorporating it into normal clinical practice.

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It is anticipated that the educational materials developed during this study will become generally available.

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# Management and outcome of chemotherapy for childhood tuberculosis

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SUMMARY The management and outcome of chemotherapy is reported for 393 children with tuberculosis notified in 1983 (191 (49%) of white, 155 (39%) of Indian, Pakistani, or Bangladeshi, and 47 (12%) of other ethnic origins). Most (313) had respiratory disease, 65 had extrathoracic lymph node disease, and 15 had both.

Only 15 (4%) of the 390 children for whom information was available did not complete chemotherapy, 10 because of default. All except 23 (6%) of the children known to have completed chemotherapy received isoniazid and rifampicin, 194 (52%) without additional drugs, 126 (34%) with ethambutol, eight (2%) with pyrazinamide, and seven (2%) with both drugs in the initial phase. The median duration of treatment was nine months.

At the time they were last seen, all except six of the 375 children who completed chemotherapy were classified by the clinician as cured either on the primary course of chemotherapy (348, 93%) or after modification for failure or relapse (11, 3%), or toxicity (10, 3%). The remaining children were still on treatment for relapse (n=2) or had defaulted from follow up (n=4).

In recent years several highly effective chemotherapy regimens of six to nine months' duration for the treatment of pulmonary tuberculosis in adults have been developed in controlled clinical trials[1] and are now being recommended for use in routine services of both technically advanced[2-5] and developing countries.[6 7] There is, in contrast, little information on the results of short course chemotherapy in children, although it is considered that, in general, the findings in adults apply to children.[8] However, ethambutol, a drug widely used in the initial phase of short course regimens based on isoniazid and rifampicin, is not recommended in young children because of the difficulties of detecting ocular toxicity.[9]

In 1978/79 the Medical Research Council Tuberculosis and Chest Diseases Unit undertook a survey of notifications of tuberculosis in England and Wales to study the characteristics of disease in both children and adults,[10 11] and also undertook a follow up of the adults with pulmonary tuberculosis to study their management.[12] A further notification survey was undertaken in 1983[13-15] and the follow up, which included both children and adults,[16] studied both management and outcome. The findings for the children with respiratory or extrathoracic lymph node tuberculosis (most of the notified cases) are reported here.

## Patients and methods

The population for this survey was based on the 401 children with respiratory disease (defined as a pulmonary lesion, a pleural effusion, or intrathoracic lymph node involvement, or any combination of the three), extrathoracic lymph node disease, or both, who were notified between 1 January and 31 December 1983, that is 89% of the 452 children in the notification survey.[15] (A further six children had respiratory or extrathoracic lymph node disease but were known to have initial resistance to one or more antituberculosis drugs and were not included as this might have affected their management.)

Approximately two years after the last child was notified, a form was sent to each clinician to obtain information on the management and outcome, in particular (a) the chemotherapy prescribed, (b) hospital admission, (c) the occurrence of adverse reactions necessitating modification of chemotherapy, and (d) the status of the child when last seen. Information was received on 399 of the 401 children but six were excluded from the analysis: one died before treatment could be started, two started treatment abroad, one developed meningitis after starting treatment (and will be reported elsewhere) and in two the notes had been lost.

Results are thus presented for 393 children. There were 313 with respiratory disease (including eight with disease involving non-respiratory sites other than extrathoracic lymph nodes) and 80 with extrathoracic lymph node disease (including 15 with respiratory disease and three with disease of other sites as well). As the management of the 15 children with both respiratory and extrathoracic lymph node disease was similar to those with extrathoracic lymph node disease alone, the findings for these two groups have been combined. There are minor differences in the number of children in some of the analyses because every item of information was not always available.

## Results

### ALL CHILDREN—PRETREATMENT CHARACTERISTICS

Of the 313 children with respiratory disease, 144 (46%) were white, 130 (42%) were of Indian, Pakistani, or Bangladeshi ethnic origin (subsequently referred to as Indian subcontinent), and 39 (12%) of other ethnic origins (table 1). Forty seven (59%) of the 80 children with extrathoracic lymph node disease were white, however, and only 25 (31%) of Indian subcontinent ethnic origin, the difference being greater for those with extrathoracic lymph node disease only (69% and 20% respectively). The annual notification rate for lymph node disease had declined since the previous survey in 1978/9 in children of Indian subcontinent ethnic origin but increased in those of white ethnic origin.[15]

Table 1 *Pretreatment characteristics*

| *Ethnic origin and age (years)* | *Type of lesion* | | | |
|---|---|---|---|---|
| | *Respiratory** | | *Extrathoracic lymph nodes†* | |
| | *No* | *(%)* | *No* | *(%)* |
| White: | | | | |
| < 5 | 48 | (33) | 17 | (36) |
| 5–9 | 41 | (28) | 20 | (43) |
| 10–14 | 55 | (38) | 10 | (21) |
| Total | 144 | (100) | 47 [2] | (100) |
| Indian subcontinent: | | | | |
| < 5 | 45 | (35) | 4 | (16) |
| 5–9 | 38 | (29) | 2 | (8) |
| 10–14 | 47 | (36) | 19 | (76) |
| Total | 130 | (100) | 25 [12] | (100) |
| Other ethnic origin‡ | | | | |
| Total | 39 | | 8 [1] | |
| Total No children | 313 | | 80 [15] | |

*Includes eight children with additional lesions: six bone or joint, one miliary, and one chest wall abscess.

†Numbers in square brackets refer to patients who also had a respiratory site involved.

‡West Indian (n=19), Chinese (n=6), African (n=3), Arab (n=1), other Asian (n=3), mixed White and West Indian (n=11), and other or mixed (n=4).

The age of distribution was broadly similar for the main ethnic groups for respiratory disease (table 1) and for the males and females. The age distribution of children with extrathoracic lymph node disease differed considerably between the ethnic groups, 21% of the 47 white children being aged 10–14 years compared with 76% of the 25 Indian subcontinent children (table 1).

Bacteriological confirmation of the diagnosis was obtained in 58 (19%) of the 313 children with respiratory disease only, 54 from respiratory specimens (usually gastric aspirate (n=30) or sputum (n=17)). A pulmonary lesion at independent radiographic assessment was present in 122 (44%) of the 277 with a radiograph available and involved an area of more than one sixth of a lung field in 34 (12%). A further 114 (41%) had enlarged intrathoracic nodes without a pulmonary lesion (but in nine (3%) a pleural effusion was present), 12 (4%) had an effusion only, and in 29 (10%) the radiograph was considered to be within normal limits. The pretreatment characteristics of the white and Indian subcontinent children were similar (data not tabulated here).

Of the 80 children with lymph node disease, bacteriological confirmation was obtained in eight (in seven from the node). In a further 46 there was histological confirmation. Of the 47 white children, only one (2%) had a positive culture from the lymph node, a further 35 (74%) having positive histology; the corresponding figures for the 25 children of Indian subcontinent ethnic origin were six (24%) and seven (28%). There were 11 (23%) white and 11 (44%) Indian subcontinent children who had neither bacteriological nor histological confirmation of the diagnosis of tuberculosis.

Of the 393 children, 249 (63%) were notified by chest physicians and 123 (31%) by paediatricians, although management may well have been undertaken jointly in some of them.

### CHEMOTHERAPY

### *Completion of chemotherapy*

Only 15 (4%) of the 390 children assessed did not complete chemotherapy (table 2), the main reason being default or poor compliance (n=10). One child died from congenital tuberculosis. In a further 58 (15%) children, chemotherapy was completed but not as planned by the clinician in charge, the com-

Table 2 *Completion of chemotherapy*

| *Chemotherapy* | *No* | *(%)* | |
|---|---|---|---|
| Not completed: | | | |
| Died | 1 | (<1) | (4) |
| Default or poor compliance | 10 | (3) | |
| Left United Kingdom | 3 | (1) | |
| Transfer (and toxicity) | 1 | (<1) | |
| Total No children completing chemotherapy | 375 | (96) | |
| Not completed as planned: | | | |
| Default or poor compliance | 21 | (5) | (15) |
| Toxicity | 10 | (3) | |
| Slow response or deterioration | 10 | (3) | |
| Error | 7 | (2) | |
| Other reasons | 10 | (3) | |
| Completed as planned | 317 | (81) | |
| Total No children assessed | 390* | (100) | |

*Information was not available for a further two children (both with respiratory disease) and in a third the lymph node was removed but no chemotherapy was prescribed.

monest reasons being default or poor compliance (n=21), toxicity (n=10), and slow response or deterioration (n=10). Thus most (81%) of the children completed chemotherapy as planned by the clinician in charge. The findings were very similar for the children with respiratory and those with extrathoracic lymph node disease.

### *Individual drugs and regimens prescribed*

All except two of the 391 children who started treatment were prescribed isoniazid, and all except nine rifampicin. Forty per cent received ethambutol, but only 5% pyrazinamide, and 4% streptomycin.

Almost all (352, 94%) of the 375 children who completed chemotherapy were prescribed regimens based on isoniazid and rifampicin (table 3); 52% had no additional drug. Over a third of the children had ethambutol as a third drug either in the initial phase only (30%) or throughout (4%). Only 15 (4%) had pyrazinamide in the initial phase, seven with ethambutol as well. The findings were similar for the children who completed chemotherapy as planned by the clinician in charge. A higher proportion of the patients with extrathoracic lymph node disease received one or two additional drugs (either in the initial phase or throughout), namely 48% compared with 35% of those with respiratory disease. There was evidence that the choice of regimen was influenced by the radiographic characteristics of the respiratory disease; for example 20 (59%) of the 34 children with a pulmonary lesion involving more than one sixth of a lung field were prescribed regimens containing ethambutol or pyrazinamide (or both drugs) in addition to isoniazid and rifampicin, compared with 38% of those with smaller pulmonary lesions and 23% of those with enlarged intrathoracic nodes only.

No child was prescribed intermittent chemotherapy.

### *Duration of chemotherapy*

Table 4 shows the distribution of the duration of chemotherapy for the children who completed chemotherapy as planned for the two regimens most commonly prescribed, namely isoniazid and rifampicin alone or with ethambutol in the initial phase. Although the median duration was nine months for both regimens there was some evidence that those not receiving ethambutol in the initial phase were treated for a shorter time (32% compared with 8%

Table 3 *Regimens prescribed*

| *Regimen* | *All children completing chemotherapy No* | *(%)* | *Children completing chemotherapy as planned* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Total No* | *(%)* | *Respiratory No* | *(%)* | *Extrathoracic lymph nodes No* | *(%)* |
| Isoniazid+rifampicin | 194 | (52) | 171 | (54) | 142 | (57) | 29 | (44) |
| Isoniazid+rifampicin+ethambutol/isoniazid+rifampicin | 111 | (30) | 96 | (30) | 73 | (29) | 23 | (35) |
| Isoniazid+rifampicin+ethambutol | 15 | (4) | 12 | (4) | 8 | (3) | 4 | (6) |
| Isoniazid+rifampicin+pyrazinamide (+ethambutol)/isoniazid+rifampicin | 15 [7] | (4) | 12 [6] | (4) | 7 [5] | (3) | 5 [1] | (8) |
| Other isoniazid+rifampicin based | 17 | (5) | 12 | (4) | 10 | (4) | 2 | (3) |
| Isoniazid+ethambutol based | 8 | (2) | 6 | (2) | 5 | (2) | 1 | (2) |
| Other | 15 | (4) | 8 | (3) | 6 | (2) | 2 | (3) |
| Total No children | 375 | (100) | 317 | (100) | 251 | (100) | 66 | (100) |

In regimens with two phases, these are separated by the /. Figures in square brackets are the number receiving ethambutol as well.

Table 4 *Duration of isoniazid+rifampicin and isoniazid+rifampicin+ethambutol/isoniazid+rifampicin regimens for children who completed chemotherapy as planned*

| *Duration (months)* | *Isoniazid+ rifampicin No (%)* | *Isoniazid+ rifampicin+ ethambutol/ isoniazid+ rifampicin No (%)* |
|---|---|---|
| ≤ 6 | 36 (21) | 4 (4) |
| 7, 8 | 18 (11) | 4 (4) |
| 9 | 59 (35) | 48 (50) |
| 10, 11 | 15 (9) | 11 (11) |
| 12 | 26 (15) | 15 (16) |
| 13–15 | 8 (5) | 4 (4) |
| >15 | 9 (5) | 10 (10) |
| Total No children assessed | 171 (100) | 96 (100) |
| Median (months) | 9·0 | 9·0 |

The duration of chemotherapy has been calculated so that, for example, nine months represents from 8·5 to 9·5 months.

Table 5 *The use of ethambutol in the initial (or only) phase for the 151 patients in whom the dosage and duration were known*

| *Duration (months)* | *No of children prescribed dosage (mg/kg)* | | | | *Total children No (%)* |
|---|---|---|---|---|---|
| | *6–12* | *13–17* | *18–22* | *23–30* | |
| ≤ 1 | 0 | 11 | 1 | 0 | 12 (8) |
| 2 | 7 | 32 | 10 | 14 | 63 (42) |
| 3 | 14 | 18 | 7 | 1 | 40 (26) |
| 4 | 0 | 4 | 2 | 0 | 6 (4) |
| 5 | 0 | 2 | 0 | 1 | 3 (2) |
| 6 | 1 | 3 | 0 | 2 | 6 (4) |
| 7–9 | 3 | 5 | 4 | 0 | 12 (8) |
| 10–12 | 5 | 1 | 1 | 0 | 7 (5) |
| >12 | 2 | 0 | 0 | 0 | 2 (1) |
| Total No children assessed | 32 | 76 | 25 | 18 | 151 (100) |

receiving less than nine months chemotherapy). The smaller number of children with extrathoracic lymph node disease were, on average, treated for longer with each regimen than those with respiratory disease.

### *Daily drug dosages prescribed*

*Ethambutol*—Of 151 children prescribed ethambutol in the initial (or only) phase, 30% were aged less than 5 years (4% less than 1 year, 9% (in all) less than 2 years), 25% were 5–9 years, and 46% were 10–14 years. The duration of treatment with ethambutol was more than 2 months in 50% and more than six months in 14% (table 5). A dosage of more than 17 mg/kg was prescribed for 43 children (28%), in 18 of them for three months or more.

*Isoniazid*—Of the 375 children prescribed isoniazid and for whom the dosage was recorded, 15% were prescribed 2–5 mg/kg, 45% 6–8 mg/kg, 33% 9–11 mg/kg, 4% 12–14 mg/kg, and 3% 15–21 mg/kg. There was evidence that higher dosages were prescribed for the younger children, 18% of the 127 aged less than 5 and 20% of the 109 aged 5 to 9 years being prescribed more than 10 mg/kg compared with 3% of the 139 aged 10 to 14 years.

*Rifampicin*—Of the 365 children who were prescribed rifampicin and for whom the dosage was recorded, 5% received 4–7 mg/kg, 38% 8–12 mg/kg, 36% 13–17 mg/kg, 20% 18–22 mg/kg, and 1% 23–25 mg/kg. There was evidence that younger children were, on average, prescribed higher dosages: 49% of the 123 children aged less than 5 years received more than 15 mg/kg compared with 37% of 106 aged 5 to 9 and 15% of 136 aged 10 to 14 years.

### *Adverse reactions*

In all, 11 (3%) of the 390 children for whom information was available were reported to have adverse reactions necessitating modification of their chemotherapy. No child had more than one type of reaction. Five children had vomiting, two had abnormal liver function tests without symptoms of hepatitis, three had rashes, and one developed possible ocular toxicity (it was not possible to determine whether or not this was confirmed at ophthalmological assessment). In six children one or more drugs were stopped, in three treatment was interrupted, and in two the drug dosage was reduced.

### INITIAL HOSPITAL ADMISSION

Less than half (46%) of the 313 children with respiratory disease were admitted to hospital initially compared with 75% of the 80 with extrathoracic lymph node disease. For both groups the main reason for admission was for investigation and diagnosis (77% and 95% respectively). For those with respiratory disease, other main reasons were severity of disease (5%), emergency (4%), and social factors (3%).

Hospital stay was reported to be prolonged for reasons other than tuberculosis in 14 (10%) of the children with respiratory disease and three (5%) of those with extrathoracic lymph node disease, the main reasons being coexisting disease (n=6) and social reasons (n=6).

The median duration of hospital stay for tuber-

Table 6 *Duration of hospital stay**

| *Duration* | *Type of lesion* | |
|---|---|---|
| | *Respiratory No (%)* | *Extrathoracic lymph nodes No (%)* |
| ≤ 7 days | 49 (41) | 36 (67) |
| 8–14 days | 36 (30) | 10 (19) |
| 15–21 days | 11 (9) | 4 (7) |
| 22–28 days | 12 (10) | 0 (0) |
| > 4 weeks | 12 (10) | 4 (7) |
| Total No children admitted | 120 (100) | 54 (100) |
| Median duration | 9 days | 4 days |

*Restricted to children for whom admission was not prolonged for reasons other than tuberculosis and for whom the duration of admission was known.

Table 7 *Outcome in children who completed chemotherapy*

| *Outcome* | *Type of lesion* | |
|---|---|---|
| | *Respiratory No (%)* | *Extrathoracic lymph nodes No (%)* |
| Cured: | | |
| On primary chemotherapy | 278 (93) | 70 (93) |
| After modification of chemotherapy for: | | |
| Slow response | 6 (5) | 2 (7) |
| Deterioration | 2 | 0 |
| Relapse | 1 | 0 |
| Toxicity | 7 | 3 |
| Not yet cured: | | |
| Still on treatment for relapse | 2 (1) | 0 (0) |
| Inadequate follow up | 4 (1) | 0 (0) |
| Total completing chemotherapy | 300 (100) | 75 (100) |
| Chemotherapy not completed | 11 | 4 |

culosis (table 6) was only four days for children with extrathoracic lymph node disease compared with nine days for those with respiratory disease, 15% and 29% respectively being in hospital for more than two weeks.

### OUTCOME OF CHEMOTHERAPY

#### *Duration of follow up*

The date of last attendance was known for 366 of the 375 children who completed chemotherapy; 15% were last seen at the time chemotherapy was completed, 27% within 6 months after completion, 31% from six to 12 months, 16% from 12 to 18 months, and 11% more than 18 months. Some of the children had been discharged from follow up but many were still attending.

#### *Outcome in the children who completed chemotherapy*

Most (93%) of the 300 children with respiratory disease were classified by the clinician as cured on the primary chemotherapy (table 7) and a further 5% after modification of chemotherapy. There were 11 children who could be considered to be therapeutic failures because they had modification of chemotherapy or a further course for slow response, deterioration, or relapse, although nine were classified as cured when last seen. In at least two of the 11, poor compliance was considered to have contributed to the therapeutic failure. Of the six children whose chemotherapy was modified because of a slow response to treatment, three had persisting enlargement of the hilar nodes with middle lobe consolidation (n=1) or partial obstruction of the right main bronchus (n=1) or trachea (n=1); the last patient was also prescribed steroids. One patient had a large effusion that was slow to resolve; chemotherapy was modified and steroids were added. The remaining two patients were reported to be slow to respond clinically. Two children had chemotherapy modified because of clinical and radiographic deterioration and three relapsed after stopping chemotherapy.

Only five of the 75 children with extrathoracic lymph node disease were not classified as cured on the primary course of chemotherapy (table 7). Two had modification of the chemotherapy for slow response, one because of persisting lymphadenopathy (who also received steroids) and one because of lack of clinical improvement with weight loss. Three children had chemotherapy modified for toxicity. Although 16 of the 75 children who completed chemotherapy were reported to have residual palpable lymph nodes when last seen, none of these were considered to be clinically important.

### CLINICAL COURSE OF EXTRATHORACIC LYMPH NODE LESIONS

Of the 80 children with lesions, 25 (31%) had an abscess or sinus on admission, the proportion being higher for the white (18, 38%) than for the Indian subcontinent children (three, 12%). A further seven (9%) developed an abscess or sinus for the first time after starting treatment (five (11%) of the white and one (4%) of the Indian subcontinent children). One or more nodes increased in size during chemotherapy in five (6%) children and new nodes appeared in 11 (14%).

### CORTICOSTEROIDS

Corticosteroids were prescribed for seven (2%) of the 393 children for reasons associated with their tuberculosis; four for persistently enlarged lymph nodes (two with hilar nodes resulting in collapse of the right upper lobe in one and the right middle lobe in the other, one with enlarged paratracheal nodes resulting in severe tracheal compression, and one with both paratracheal and cervical nodes). Two children had pleural effusions and the seventh child had respiratory disease which was slow to respond to chemotherapy. Four of the seven children also had modification of their antituberculosis chemotherapy (see above).

### OTHER DISEASES

In all, 41 of the 393 children were reported to have one or more coexisting diseases, the commonest being asthma in 19. Six children had anaemia, three had congenital heart lesions (one coarctation of the aorta and two ventricular septal defects), one had Down's syndrome, one thalassaemia, one haemohilia, and three had other congenital abnormalities. Other diseases, each occurring in one child, were bronchiectasis, coeliac disease, epilepsy, encephalitis, and diabetes, and two were reported to have unspecified psychiatric illnesses.

### FACTORS AFFECTING MANAGEMENT

Stepwise multiple regression analysis restricted to children notified by chest physicians or paediatricians (95% of the children) were used to examine possible associations between pretreatment factors and patient management. The independent variables studied were age, sex, ethnic origin, the results of smear examination and of culture of sputum, the presence of a pulmonary lesion or enlarged intrathoracic nodes at independent assessment, whether notified by the paediatrician or chest physician, and the type of lesion (respiratory or extrathoracic lymph node).

An analysis of the total duration of chemotherapy based on 288 children who completed chemotherapy as planned and were prescribed regimens based on isoniazid and rifampicin identified four significant factors associated with a longer duration of chemotherapy, namely, notified by a paediatrician, a positive culture, extrathoracic lymph node disease, and Indian subcontinent ethnic origin.

Duration of hospital stay in the 174 children admitted initially and whose stay was not prolonged for reasons other than tuberculosis was significantly associated with two factors, namely the diagnosis of respiratory disease and a pulmonary lesion at independent assessment (both associated with a longer duration).

In neither the analyses of duration of chemotherapy nor those of hospital stay did the independent variables account for more than 14% of the total variation and it is likely that most of the remaining variation is due to differences in methods of management of the large number of clinicians involved.

## Discussion

This survey has provided information on the routine management of children diagnosed as suffering from respiratory or extrathoracic lymph node tuberculosis in England and Wales in 1983, almost all of whom were managed by respiratory physicians or paediatricians. Information was collected at least two years after the start of treatment and the results of treatment were, on the whole, excellent. Only 4% of 390 children did not complete a course of chemotherapy, usually because of default or poor compliance, and of those completing treatment 93% were reported to be cured on the primary course of chemotherapy, a further 6% being cured after modifications, which were frequently minor.

At most, only 13 (3%) of the children could be regarded to have responded unsatisfactorily, 11 with respiratory and two with extrathoracic lymph node disease. In eight (including the two with lymph node disease) the only problem was a slow response to the initial chemotherapy. Of the remaining five, two were reported to have deteriorated during chemotherapy and three to have relapsed after stopping chemotherapy. Poor compliance was considered to have contributed to therapeutic failure in at least two of the patients and all except the two still on treatment at the time of the follow up were considered to be cured after modification of the chemotherapy or a further course.

The regimens currently recommended for the treatment of pulmonary tuberculosis in adults in England and Wales are a nine month regimen of isoniazid and rifampicin with a two month initial supplement of ethambutol,[17] or a six month regimen in which pyrazinamide is also given for the first two months.[3] The role of pyrazinamide in the initial phase in short course chemotherapy is well established in adult pulmonary disease, and the risk of hepatic toxicity in these regimens is very low. There is much less experience with pyrazinamide in children, although it has been used in children with tuberculous meningitis in Hong Kong and Madras.[18 19] In the present survey only 5% of children were given pyrazinamide initially, compared with 23% of 1068 adults with pulmonary tuberculosis notified in the first six months of 1983.[16] It will be important to assess how widely the six month regimen containing pyrazinamide becomes adopted in clinical practice in the next few years, both in children and adults and to monitor both the acceptability and toxicity in routine practice.

In the present survey the regimen most commonly prescribed for both respiratory and lymph node disease was isoniazid and rifampicin without a third drug (in 52%). In view of the low incidence of initial resistance[15] and the limited extent of disease in most children it is likely that treatment with such a regimen is adequate for most children in England and Wales and this is borne out by the results. Even in adults with extensive smear positive pulmonary disease in East Africa, a regimen of isoniazid and rifampicin for six months was highly effective with a relapse rate of only 7% in 164 patients in two years of follow up.[20] Studies in Hong Kong have shown that adult patients with smear negative pulmonary disease (whether culture positive or culture negative) and small radiographic lesions can be cured by regimens of four months' duration,[21] and this group of patients may correspond more closely to many of the paediatric cases than the more extensive, culture and frequently smear positive pulmonary disease in patients with whom short course chemotherapy has usually been investigated. The results achieved in the present survey suggest that durations of less than nine months, even without pyrazinamide, were effective.

The evidence is that the main role of ethambutol when given in addition to isoniazid and rifampicin is the prevention of the emergence of further resistance in the small proportion of patients with initial resistance to one or more antituberculosis drugs.[22] As the incidence of initial resistance to isoniazid is low in children in the United Kingdom (although higher in those of Indian subcontinent than those of white ethnic origin[15]) there is little, if any, place for ethambutol in the treatment of tuberculosis in children. Indeed, because of the risks of ocular toxicity associated with this drug and the difficulties of detecting such toxicity in children, it has been recommended that it should not be used in young children.[9] In this survey, however, only one possible case of ocular toxicity was reported in 151 children receiving the drug, many in dosages higher than those recommended and for a longer period.

Adverse reactions to the antituberculosis drugs requiring modification of chemotherapy were rare, occurring in only 11 of the 390 children for whom information was available. There were only two children who had chemotherapy modified because of abnormal liver function tests; neither had symptoms of hepatitis. In one child (aged six years) possible ocular toxicity was reported but we were unable to ascertain whether it was confirmed on ophthalmological examination. The commonest reactions were vomiting (n=5) and skin rashes (n=3). Appropriate dosages of individual antituberculosis drugs for adults are well established but there has been considerable variation in the dosages recommended for children. In the present survey there was a wide range in the dosages of isoniazid, rifampicin, and ethambutol prescribed on a mg/kg body weight basis. Although most were within an acceptable range, an appreciable proportion were prescribed dosages below or above the range. The recommended dosage of ethambutol is the same as the adult dosage but for isoniazid and rifampicin higher dosages are usually recommended. For isoniazid 10 mg/kg is the standard dosage,[23] although up to 20 mg/kg is sometimes recommended,[8] and recent reports have suggested that lower dosages may be adequate.[24] In the survey 25% of the children received dosages of 5 mg/kg or less and 4% had 15 mg/kg or more. The recommended dosage of rifampicin is 10–20 mg/kg,[8 23] and there is evidence that dosages in the higher end of the range should be prescribed in children (but not in neonates).[25] However, a study of children with tuberculous meningitis in India demonstrated that there is an appreciable risk of hepatic toxicity particularly if rifampicin is given in association with isoniazid in high dosage.[19] In the present survey, 19% of children were prescribed dosages of less than 10 mg/kg and 7% more than 20 mg/kg. For ethambutol, where dosage is of particular importance because of its association with ocular toxicity, 22% received less than 13 mg/kg and 30% more than 17 mg/kg, 12% receiving more than 17 mg/kg for more than two months. In view of the difficulty of detecting ocular toxicity in very young children, it is of particular concern that 36% of those aged less than 5 years were prescribed ethambutol.

Of the 80 children with extrathoracic lymph node disease, 6% had a temporary increase in size of one or more nodes during chemotherapy, 9% developed abscesses or sinuses, and 14% developed new nodes. None of these children were given corticosteroids, although they were prescribed for four children with persistently enlarged intrathoracic nodes. Residual lymph nodes were reported in 16 children at the time the child was last seen but none was considered clinically significant and all the children were classified as cured by the clinician. Such problems in the clinical course of lymph node disease are well known and, in a study conducted by the British Thoracic Society in adults,[26] were as common during and after treatment with an 18 month regimen of isoniazid and rifampicin as with a nine month regimen, and were rarely due to a relapse or reactivation of the tuberculosis.

Initial admission to hospital was usually for investigation and diagnosis (in just under half of the children with respiratory disease but three quarters of those with extrathoracic lymph node disease). In most of the children with lymph node disease it was related to surgical procedures and the median duration of stay for tuberculosis was only four days. In respiratory disease the median duration of admission for tuberculosis was nine days, 29% of the children being in hospital for more than two weeks and 10% for more than four weeks. Thus hospitalisation was usually for specific indications and for short periods.

This survey has shown that the results of treatment of childhood respiratory and extrathoracic lymph node tuberculosis in England and Wales in patients diagnosed in 1983 were, on the whole, excellent. Chemotherapy was based on the highly effective combination of isoniazid and rifampicin in most patients, although the high proportion of children, even of those aged less than 5 years, receiving ethambutol gives some cause for concern. However, no confirmed ocular toxicity was documented. A third drug may be desirable in circumstances where there is likely to be a high risk of initial drug resistance. Pyrazinamide has been shown to result in a more potent regimen of shorter duration in adults but experience of pyrazinamide in children is relatively limited. The evidence is that it is well tolerated,[18 19] and has a low incidence of side effects, and therefore its use should be considered as a third drug in the initial phase of chemotherapy even in young children. Recent recommendations about the treatment of tuberculosis in adults and children have recommended the use of chemotherapy based on isoniazid, rifampicin, and pyrazinamide,[4 8] and the Joint Tuberculosis Committee of the British Thoracic Society is currently preparing a similar recommendation for Britain.

The survey was undertaken by Mr AJ Nunn, Mr SP Byfield, Dr JH Darbyshire, and Professor W Fox, Medical Research Council Tuberculosis and Chest Diseases Unit, Dr KM Citron (consultant physician) and Dr JO Warner (consultant paediatrician), Brompton Hospital. Radiological assessments were made by Dr M Caplin. The contribution of the Communicable Disease Surveillance Centre (Dr NS Galbraith) and the Mycobacterium Reference Unit (Dr PA Jenkins) of the Public Health Laboratory Service was coordinated by Dr ON Gill.

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# Acquired cerebral palsy

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The heterogeneity associated with the diagnostic label of cerebral palsy has led to the formulation of several definitions of the syndrome. Early reports by Little, Osler, and Freud described cerebral palsy not as a disease entity but as a collection of motor disorders dating from the time of birth or early childhood and due to lesions of the brain.[1] The current burgeoning of interest in the epidemiology of the cerebral palsies has been largely instigated by its possible use as an outcome measure of the effectiveness of neonatal intensive care. This interest has drawn attention to some of the differences in, for example, the definitions given by the Little Club of London,[2] Bax,[3] and Nelson and Ellenberg.[4] It is common to these definitions that the lesion is of the brain, is non-progressive, and leads to a motor disorder resulting in aberrant posture and control. Some of the variation in definition is associated with the timing of the presumed insult, which may be in the early years of life,[2 4] or of the immature brain.[3]

In examining the epidemiology of cerebral palsy, the present tendency is to separate those in whom the presumed aetiology is postnatal—that is, 'acquired'—from those where the aetiology is prenatal or perinatal in origin. This report is an account of the epidemiology of acquired cerebral palsy in the Mersey region.

## Methods

A register was compiled of all cases of cerebral palsy born in the years 1966–77, whose mother's area of residence at the time of birth was within the boundary of the Mersey regional health authority, which has a total population of approximately 2·5 million. Several sources of data were used to compile the register, these included the handicap registers maintained in each district health authority, the national Rowntree Trust register of all families claiming a family disability allowance, records of all children attending schools for the educationally subnormal (moderate and severe) and the physically handicapped, and a search by the Office of Population Censuses and Surveys for all death certificates in which the underlying cause of death on Part I, or as other significant condition contributing to the death on Part II, of the certificate was cerebral palsy.

The definition of cerebral palsy used was that proposed by Bax, namely a non-progressive group of disorders of movement and posture due to a defect or lesion of the immature brain. Because the definition only includes non-progressive disorders and lesions of the immature brain, all cases in which the underlying pathology was a tumour or a lesion of the spinal cord were excluded. The cerebral palsy was classified as acquired if the damage to the brain was considered to have taken place after the 28th postnatal day and up to the end of the 5th year.

The categorisation of the type of cerebral palsy was made on the basis of information in the clinical records of each child. If there was uncertainty about the timing of the insult, the aetiology was presumed congenital and not acquired.

The cases were grouped into spastic quadriplegia, spastic hemiplegia, and 'others'. Spastic quadriplegia included quadriplegia, double hemiplegia, and mixed quadriplegia and double hemiplegia. Spastic hemiplegia included the mixed hemiplegias. Others included the dyskinesic, ataxic, hypotonic, mixed spastic diplegic, and unclassified types of cerebral palsy.

The severity of functional disability as it affected ambulation was classified as minimal, moderate, or severe. Minimal disability meant that the child required no aid for walking though aid for climbing stairs may have been necessary. Moderate disability involved the use of an aid to enable the child to be mobile, either crutches or a self propelled wheelchair. Severe disability necessitated the use of a wheel chair that was not self propelled.

Almost all children were assessed by a clinical or educational psychologist at least once, usually when school placement was being considered. A variety of assessment procedures was used. Where possible mental disability was graded according to the intelligence quotient (IQ). Severe retardation was determined by an IQ $<50$, moderate retardation by an IQ 50–69, and normal or minimal retardation by an IQ $\geqslant 70$.

## Results

There were 833 cases of cerebral palsy recorded in the register of which 147 (18%) were classed as acquired—that is, the brain damage was considered to have taken place after the 28th day of life and up to the end of the 5th year. These 147 cases are the index cases for this report, 82 were boys and 65 were girls, a male:female ratio of 1.3:1. The cases relate to a denominator population of 443 531 survivors of the neonatal period giving an incidence of acquired cerebral palsy of 3·31/10 000. There was no discernible trend in incidence over time, the annual incidence rate by year of birth is shown in table 1.

### TYPE OF CEREBRAL PALSY

Spastic quadriplegia with 76 cases (52%) was the commonest type of acquired cerebral palsy. There were 61 cases (41%) of spastic hemiplegia. 'Others' included 10 cases which were comprised of ataxia (n=3), dyskinesia (n=2), hypotonia, spastic diplegia, and mixed type (one case each), and there were two cases in whom the type of cerebral palsy was not recorded.

### AETIOLOGY

The presumed cause of the cerebral palsy was grouped using a similar classification to that of Blair and Stanley and is shown in table 2.[5] The commonest causal group was infection, which consisted predominantly of infections of the brain or meninges. A significant number of cases, however, were attributed to circulatory collapse consequent upon other infections such as septicaemia, respiratory tract infections, and shigella dysentery.

The age at which the damage to the brain occurred differed according to the causal group. As might be expected, head injury after a road traffic accident was more common in the older child, 12 out of 13 cases were incurred after the 2nd birthday. In contrast, non-accidental injury took place early in life with 11 out of 12 cases occurring within 18 months of birth. Acquired cerebral palsy attributable to infections was distributed throughout the first five years but was predominantly in the first year (34/63, 54%) and 27% in the second year. Gastroenteritis and dehydration as the causal factor showed an even greater preponderance in the first year when 20 out of 22 cases (91%) occurred. In five cases the onset of the cerebral palsy was noted to have followed the administration of pertussis vaccine. The time relationship was not stated, however, and cause and effect cannot be assumed.

Table 1 *Incidence of acquired cerebral palsy by year of birth*

| *Year of birth* | *No of cases* | *No of neonatal survivors* | *Incidence/10 000 neonatal survivors* |
|---|---|---|---|
| 1966 | 15 | 44 485 | 3·37 |
| 1967 | 22 | 42 982 | 5·12 |
| 1968 | 8 | 42 529 | 1·88 |
| 1969 | 11 | 41 242 | 2·67 |
| 1970 | 8 | 40 982 | 1·95 |
| 1971 | 17 | 40 170 | 4·23 |
| 1972 | 21 | 36 973 | 5·68 |
| 1973 | 12 | 33 552 | 3·58 |
| 1974 | 14 | 32 113 | 4·36 |
| 1975 | 5 | 30 885 | 1·62 |
| 1976 | 8 | 29 472 | 2·71 |
| 1977 | 6 | 28 146 | 2·13 |
| Total | 147 | 443 531 | 3·31 |

Table 2 *Acquired cerebral palsy grouped by cause*

| *Apparent cause* | *No* | *(%)* |
|---|---|---|
| Head injury: | | |
| Road traffic accident | 13 | (8·8) |
| Non-accidental | 12 | (8·2) |
| Other head injury | 10 | (6·8) |
| Anoxia: | | |
| Suffocation | 3* | (2·0) |
| Electrocution | 1 | (0·7) |
| Postoperative cardiac arrest | 3 | (2·0) |
| Postepileptic | 13† | (8·8) |
| Cerebrovascular accident | 5 | (3·4) |
| Gastroenteritis and dehydration | 22 | (15·0) |
| Infections | 63 | (42·9) |
| Miscellaneous | 2 | (1·4) |
| Total | 147 | 100% |

*One case non-accidental; †one postoperative.

There were 13 cases in whom the cerebral palsy was classified as postepileptic. Although in all but one it is unlikely that convulsions caused the brain damage. Thus in eight of these cases the presenting feature was convulsions in infancy, and the cerebral palsy was diagnosed subsequently. It is difficult to be certain of cause and effect in these cases as an underlying pathology may have been responsible for both the epilepsy and the cerebral palsy. In a further two cases convulsions were associated with hypernatraemia and severe dehydration. In one child hypoxic brain damage was diagnosed after admission to hospital aged 7 weeks with recurrent fits and severe hypothermia, in another the cerebral palsy was attributed to convulsions and cardiac arrest which occurred postoperatively and there was only one case in which cerebral palsy was attributed to prolonged generalised convulsions when aged 3.

### MOTOR AND MENTAL DISABILITY

The association between motor and mental disabil-

Table 3 *Correlation of mental and motor disability*

| *Motor disability (ambulation)* | *No (%) with mental disability* | | | *Total* |
|---|---|---|---|---|
| | *Normal or minimal* | *Moderate* | *Severe* | |
| Minimal | 30 (86) | 20 (77) | 16 (20) | 66 (46) |
| Moderate | 5 (14) | 5 (19) | 7 (9) | 17 (12) |
| Severe | 0 (0) | 1 (4) | 58 (72) | 59 (42) |
| Total | 35 (100) | 26 (100) | 81 (100) | 142 (100)* |

*Data on mental or physical disability not available for five cases.

ity is shown in table 3. A higher proportion of children show severe mental retardation as classified by the criteria in this study. A child with acquired cerebral palsy whose mobility is severely affected is almost invariably severely mentally retarded also but the converse does not hold true. These differences are reflected in the type of school attended. Sixteen (11%) of the 147 children were attending a normal school, 33 (22%) a school for the physically handicapped and 67 (46%) a school for the educationally subnormal (ESN). Of the 67 most (56) were at an ESN (severe) school. A further 24 children were not at school because they had died before attaining school age or because they were too young to be attending school.

Tables 4 and 5 show the severity of mental and motor disability respectively associated with the type of cerebral palsy. As would be expected, the children with quadriplegia suffer a significantly greater degree of mental retardation and functional motor disability than the hemiplegias. Even among those with hemiplegia, moderate or severe mental retardation predominates, occurring in 32 of 59 cases, whereas functional motor disability is much less evident almost all being mobile without requiring aid.

Table 4 *Mental disability according to type of cerebral palsy. Results are No (%)*

| *Mental disability* | *Type of cerebral palsy* | | |
|---|---|---|---|
| | *Spastic hemiplegia* | *Spastic quadriplegia* | *Others* |
| Normal/minimal | 27 (46) | 6 (8) | 2 (25) |
| Moderate | 16 (27) | 8 (11) | 2 (25) |
| Severe | 16 (27) | 61 (81) | 4 (50) |
| Total | 59 (100) | 75 (100) | 8 (100) |

Table 5 *Motor disability according to type of cerebral palsy. Results are No (%)*

| *Motor disability* | *Type of cerebral palsy* | | *Others* |
|---|---|---|---|
| | *Spastic hemiplegia* | *Spastic quadriplegia* | |
| Minimal | 52 (88) | 10 (13) | 5 (63) |
| Moderate | 3 (5) | 13 (17) | 1 (13) |
| Severe | 4 (7) | 52 (69) | 2 (25) |
| Total | 59 (100) | 75 (100) | 8 (100) |

### BIRTHWEIGHT SPECIFIC INCIDENCE OF ACQUIRED CEREBRAL PALSY

Among the cases of acquired cerebral palsy, 11% were of low birth weight (<2500 g) compared with 6·1% of all neonatal survivors—that is, the risk of a child acquiring cerebral palsy is almost double in the low birthweight infant. In contrast, there is almost a seven fold increase in risk for congenital cerebral palsy in low birth weight compared with normal birthweight infants.[6] Birthweight specific rates for acquired and congenital cerebral palsy are shown in table 6.

## Discussion

Most definitions of cerebral palsy refer to the condition being the result of damage to the immature brain. Crucial to this definition is the age at which the brain is no longer considered immature. Blair and Stanley included those cases where the potentially brain damaging event had been recorded before the age of 5 years.[5] On the other hand Cussen *et al* include cases up to the age of 2 years,[7] while Swinyard *et al,* in a study from New York, take the upper limit as 15 years.[8] These differences in definition will profoundly affect the relative preponderance of the casual factor, the older the age limit at which the brain damage occurs the greater the relative importance of road traffic accidents in particular.

There is similar variation in the age at which the insult occurs for differentiating between 'congenital' and 'acquired' cerebral palsy.[5] Blair and Stanley included individuals born free of brain damage who

Table 6 *Birthweight specific rates of acquired and congenital cerebral palsy*

| *Birth weight (g)* | *Acquired cerebral palsy* | | *Congenital cerebral palsy* | |
|---|---|---|---|---|
| | *No of cases* | *Prevalence/10 000 neonatal survivors* | *No of cases* | *Prevalence/10 000 neonatal survivors* |
| ≤1500 | 1 | 7·1 | 35 | 270·7 |
| 1501–2500 | 13 | 5·6 | 145 | 62·4 |
| >2500 | 117 | 3·1 | 440 | 11·7 |

These rates exclude infants born in 1966 because of lack of birthweight specific denominator data for that year. The data for the congenital cerebral palsy have been previously published.[6]

suffered some subsequent potentially brain damaging event which was unrelated to a perinatal cause. Others draw the dividing line at 7 days,[7] 14 days,[8] or 28 days after birth.[4 9] As the clinical diagnosis of cerebral palsy is not made in most cases until some months or even years after birth, it is often not possible to be certain when the brain damaging event took place. This uncertainty is greatest when the presumed insult is in the perinatal period. For example, in a premature and small for dates infant that has a stormy intrapartum and early neonatal history and is subsequently found to have cerebral palsy, it may be difficult to distinguish cause and effect. Modern investigative procedures such as ultrasound scanning may help to narrow the uncertainty. Even in the older child, when the developmental delay is only recognised after a serious infective episode, there may occasionally be uncertainty in determining cause and effect.

In the study reported here, the observation that 18% of cases of cerebral palsy are acquired is significantly higher than that from several other studies where the proportion ranges from 3–13%.[10] Several factors may be responsible, apart from the differences in the definition of timing of an insult, there are variations in the methods by which cases are ascertained and in the population from which they arise. These differences in definition and ascertainment bedevil all epidemiological studies of cerebral palsy and render invalid almost all comparisons between studies. Standardisation of data recording is an essential step in solving these issues and a step in the right direction has been made.[11]

It is pertinent to comment on the recorded association of pertussis vaccination and cerebral palsy. These cases were diagnosed at a time when there was intense interest and speculation on the neurological sequelae attributable to pertussis vaccination. The fact that five cases of cerebral palsy in the survey reported here were noted to follow vaccination must be interpreted with caution. Clear documentation of the time relationship between the two events was not available and a causal association is not a valid assumption.

The major tragedy of acquired cerebral palsy is that a considerable proportion of cases is potentially preventable. Furthermore, comparing the severity of mental retardation in congenital cerebral palsy reported in an earlier paper[12] with these data on acquired cerebral palsy, the latter show a significantly higher proportion of cases with severe or moderate mental retardation. This has important implications for health and social service provision and for the burden of care experienced by the family of an affected child.

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# Screening for Duchenne muscular dystrophy

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SUMMARY A programme was introduced in Wales to screen all 18 month old boys who were not yet walking for raised creatine kinase activity within the existing community developmental screening programme. During an 18 month period 25 229 such boys were identified of whom 19 930 (79%) had a Denver developmental screening test and 338 (1·7%) of these were not walking. Two hundred and five of those who did not walk (61%) had creatine kinase activity assayed and two cases of Duchenne muscular dystrophy were detected.

We conclude that screening boys of 18 months who do not walk is worthwhile if the opportunity arises, but that a population based screening programme of this type is not justified as detection rates will be unacceptably low.

Duchenne muscular dystrophy is a serious X linked recessive disorder for which there is no treatment. It is the commonest of the muscular dystrophies with an incidence of about 1 in 4000 male births.[1 2] Recently there have been great advances in the understanding of the molecular genetics of Duchenne muscular dystrophy and accurate and reliable antenatal diagnostic tests are now available for carriers of the disease.[3–5] Now that the defect in the basic protein has been recognised, there must be hope that treatment will follow.[6] Discovering whether or not the female relatives of affected boys are carriers, together with prenatal diagnosis, are the principal methods of preventing Duchenne muscular dystrophy. These can be improved by careful family studies and the use of genetic registers. Early diagnosis of affected boys is crucial, as the earlier that carriers among female relatives are discovered the greater the opportunity for preventing secondary cases. Despite the importance of early diagnosis the mean age at diagnosis for new cases often remains unsatisfactorily late.[7–9]

Detection of new cases at birth is feasible by newborn screening of all boys.[10–13] This has not found general favour because, as there is no treatment at present for Duchenne muscular dystrophy, it does not fulfil the traditional requirements.[14] It has, however, been justified on financial grounds as the creatine kinase assay used is cheap, and prevention (compared with management) is cost effective.[15 16] As a compromise Gardner-Medwin *et al* proposed that screening might be restricted to boys who are not walking by the age of 18 months.[9] This age was selected because 97% of normal boys are walking,[17] whereas only 50% of boys with Duchenne muscular dystrophy are doing so.[8] This would mean fewer tests and less anxiety for parents, particularly as their concern regarding development might already be aroused by the delay in walking.

We report our experience of setting up and running a screening programme for Duchenne muscular dystrophy covering the whole of Wales in which all boys unable to walk four independent steps by the age of 18 months were tested by having creatine kinase assays carried out on blood taken by finger print sampling.

## Patients and methods

The screening programme was coordinated by a specialist nurse in this department who was supported by a clinical geneticist, a consultant paediatrician, a clinical research fellow, and the principal scientist responsible for the regional newborn screening programme. Before starting the programme all health authorities were visited and an initial discussion between the chief administrative medical officer of the district, the nursing administration, and the project staff was held to discuss the aims and protocol of the programme. Subsequently the team was invited back to some districts for further discussion with general practitioners, health visitors, and the community medical services. The project was discussed with consultant paediatricians through the Welsh Paediatric Society, and ethical permission was obtained from the relevant bodies.

The screening programme was based on the routine Denver developmental screening test[18 19] that should be performed on all children in Wales by the health visitor. Incorporated into this was a simple item that elicited whether or not the boys could walk four independent steps. The age at which different health authorities performed this screening varied. Those districts that screened with the Denver test earlier than 18 months arranged to reassess boys who were not walking again at that age. If they failed this initial screening test they were referred to the local community paediatric service for a general assessment.

At this consultation the family was counselled about the possibility of muscular dystrophy and the boy offered a finger prick blood test for creatine kinase. This was taken on the same filter papers used for newborn phenylketonuria screening and was posted to the newborn screening laboratory at the Institute of Medical Genetics where the assay was performed. All results were communicated to the community paediatric service. Positive results were confirmed on a sample of venous blood taken by the local consultant paediatrician or general practitioner. Referral to a paediatric neurologist was then arranged for repeat serum creatine kinase assay, muscle biopsy, and electromyography to confirm the diagnosis. After confirmation of the diagnosis genetic counselling was offered and extended family analysis performed.

The programme was monitored using computer data obtained from the Welsh Health Common Services Authority. This computer has a record of all children born in Wales and provided the numbers of 18 month old boys in each district. As part of the screening programme each health authority was sent each month a list of all the boys in that area that would reach the age of 18 months during that month. These were then issued to the health visitors who returned the computer print out indicating which boys had been screened and which were not walking four independent steps. These were collected by a person nominated locally to be in charge of the screening programme, and then sent to the central coordinating officer. From this monitoring system the following figures were obtained for each area: the number of 18 month old boys; the number who had undergone the Denver test; the number not walking; the number who had had a creatine kinase assay; the number of positive tests; and the number diagnosed as having Duchenne muscular dystrophy.

All the boys diagnosed during this study period were assessed with the Griffiths's mental development scales.[20]

All other cases of Duchenne muscular dystrophy diagnosed clinically and born during the dates of the cohort studied were identified through genetic counselling services provided throughout Wales.

### BIOCHEMICAL METHOD

Creatine kinase was measured fluorimetrically on a 0·5 cm spot punched from the finger prick filter paper specimen. The assay was in a final volume of 200 μl containing the following: glucose 20 mmol/l; magnesium acetate 10 mmol/l; adenosine diphosphate 3 mmol/l; nicotinamide adenine dinucleotide phosphate 2 mmol/l; diadenosine pentaphosphate 440 μmol/l; hexokinase 2500 U/l and glucose-6-phosphate dehydrogenase 3000 U/l in imidazole buffer 100 mmol/l, pH 6·7. The blood spot was eluted for one hour at 30°C in 200 μl of reaction mixture without substrate. Creatine phosphate was added in a 20 μl volume and the incubation continued for 30 minutes; 100 μl were diluted to 2 ml with carbonate buffer (500 mmol/l, pH 11·0) and the fluorescence of the reduced form of nicotinamide adenine dinucleotide phosphate in this solution was measured.

Blood samples from both normal and affected boys were assayed concurrently and creatine kinase Lin-Trol (Sigma) was used as a creatine kinase standard. The method gave a normal range with a mean (SD) of 163 (98) U/l, n=205, range 0–385 U/l, during the 18 month period for which data are complete. The three cases detected gave values of 6685, 5274, and 9005 U/l, respectively.

## Results

This study ran for two years from January 1986 to January 1988 and concerned boys born between July 1984 and July 1986 (table 1). To make the programme operational required considerable effort and there was initial resistance in some districts. Because of this the data are not complete for the first six months.

Taking the 18 month period July 1986 to January 1988 (screening boys born between 1 January 1985 and 1 July 1986) where full returns are available, 25 229 boys were identified from the computer returns. The returns indicated that 19 930 of these (79%) had had the Denver developmental screening test and of these 338 (1·7%) were not walking. Two hundred and five of the 338 (61%) of the boys who were not walking had a creatine kinase test.

There was, however, considerable variation between districts. One district screened 89% of boys with the Denver test and 76% of those who were not walking with the creatine kinase assay. Another district only screened 27% with the Denver test

Table 1 *Data for 18 month period 1 July 1986 to 1 January 1988*

| *District* | *No of 18 month old boys* | *Percentage who had Denver test* | *Percentage not walking* | *Percentage tested for creatine kinase* |
|---|---|---|---|---|
| 1 | 3726 | 89 | 1·9 | 76 |
| 2 | 1784 | 53 | 2·0 | 136 |
| 3 | 3229 | 72 | 1·5 | 86 |
| 4 | 2017 | 67 | 2·0 | 52 |
| 5 | 5114 | 94 | 1·6 | 53 |
| 6 | 973 | 27 | 1·5 | 100 |
| 7 | 950 | 76 | 1·9 | 64 |
| 8 | 4210 | 85 | 1·6 | 44 |
| 9 | 3226 | 84 | 1·7 | 83 |
| Total No | 25229 | | | |
| Mean value | | 79 | 1·7 | 61 |

according to the computer returns, but did screen all those who were not walking (albeit only 4). One district, despite testing 84% with the Denver test, only tested 16% of those who were not walking with the creatine kinase assay. One district sent in more creatine kinase tests than the recorded number of boys who were not walking.

In the 18 month period for which complete data are available two boys were diagnosed through the screening programme. Three other boys in the cohort were diagnosed clinically as having Duchenne muscular dystrophy before screening at 18 months.

In the full two year study three boys were identified as having Duchenne muscular dystrophy through the screening programme, and four boys with Duchenne muscular dystrophy born between 30 June 1984 and 30 June 1986 were also identified, giving a total of seven cases identified in the two year cohort. The case histories of these seven cases are summarised below. The developmental quotients obtained on the Griffiths's mental development scales are shown in table 2.

Table 2 *Subscale quotients on the Griffiths's mental development scale*

| | *Case No* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* |
| Age at assessment (months) | 29 | 26 | 18 | 23 | 23 | 14 | 33 |
| Locomotor | 51 | 80 | 80 | 74 | 85 | 84 | 64 |
| Personal and social | 58 | 73 | 86 | 60 | 83 | 85 | 91 |
| Hearing and speech | 53 | 65 | 53 | 52 | 76 | 82 | 91 |
| Eye and hand coordination | 68 | 75 | 89 | 65 | 80 | 90 | 95 |
| Performance | 68 | 71 | 78 | 60 | 96 | 92 | 97 |
| General quotient | 60 | 73 | 83 | 62 | 84 | 88 | 90 |

### CASE REPORTS OF BOYS DIAGNOSED THROUGH SCREENING PROGRAMME

*Case 1*

This boy was the second boy in the family. He was sitting without support at 8 months, cruising at 18 months, and not walking four independent steps until 28 months. When the diagnosis was made his older brother was also suspected as having Duchenne muscular dystrophy at the age of 5 years 6 months, and had obvious clinical features of the disease. Venous creatine kinase activities for both boys were grossly raised at 15 650 U/l (case 1) and 12 450 U/l, respectively. Muscle biopsy and electromyography on the older brother confirmed the diagnosis. On analysis of DNA both boys show deletions with c-DNA probe cf56A, permitting specific prenatal diagnosis in a future pregnancy.

*Case 2*

This boy was an only child who sat up unaided at 6 months, crawled at 10 months on his front, and at 12 months on his knees. He was standing with support at 12 months, walking with support at 14 months, and walking independently at 20 months. On examination he was generally hypotonic with no pseudohypertrophy or other specific abnormal signs. Creatine kinase activity was raised at 15 750 U/l, electromyography and muscle biopsy confirmed the diagnosis. The mother's risk of being a carrier is 46% based on creatine kinase and pedigree analysis. Analysis of DNA has so far not shown a deletion.

*Case 3*

This boy was an only child who sat unsupported at 10 months, crawled at 12 months, was standing with support at 15 months, and walking independently at 19 months. On examination no specific abnormalities were detected, but he died suddenly at home while asleep. The creatine kinase activity was 9005 U/l and a muscle biopsy taken at necropsy confirmed the diagnosis. The cause of death was aspiration, thought to have occurred during a febrile convulsion. The mother's risk of being a carrier is 99% based on creatine kinase and pedigree data. No DNA was available for analysis.

### CASE REPORTS OF BOYS DIAGNOSED CLINICALLY

*Case 4*

This boy's disease was diagnosed at the age of 18 months with his older brother who had been investigated for developmental delay and clumsiness at the age of 3 years 6 months. He was walking at 15 months and his older brother at 18 months. Creatine kinase activity was raised at 8600 U/l. A creatine kinase activity of 9450 U/l, muscle biopsy and electromyography on the older boy confirmed the diagnosis. DNA analysis of the two boys has so far not shown any deletion.

*Case 5*

This boy's disease was diagnosed at the age of 10 months when he was being investigated for failure to thrive. He was sitting unsupported at 10 months and walked unaided at 18 months. The creatine kinase activity was 15 200 U/l, electromyography and muscle biopsy confirmed the diagnosis. The mother's risk of being a carrier is 99% based on creatine kinase and pedigree data. DNA analysis showed a deletion with c–DNA probe cf56A.

*Case 6*

This boy's disease was diagnosed at the age of 1 year. He was sitting unsupported at 6 months but not walking unaided until 20 months. The mother, who had a brother with Duchenne muscular dystrophy was a potential carrier and had received genetic counselling but had not had antenatal diagnostic tests. A creatine kinase estimation was done at the mother's request when he was 1 year old, and was raised at 7620 U/l. The mother is an obligate carrier. DNA analysis has so far failed to show a deletion.

*Case 7*

The boy was the first boy in the family, and had an older sister. He was sitting without support at 9 months, cruising at 10 months, and walking without help at 17 months. He was investigated as he was considered to be late walking at 17 months. Creatine kinase activity was raised at 14 562 U/l and diagnosis was confirmed by muscle biopsy and electromyography. The mother's risk of being a carrier is 36% based on creatine kinase and pedigree data. DNA analysis has so far failed to show a deletion.

## Discussion

During the 18 months that the screening programme was running fully, one can estimate from the population statistics that theoretically seven boys should have been born with Duchenne muscular dystrophy. Five have already been discovered, two through the screening programme (cases 2 and 3) and three on clinical grounds (cases 5, 6, and 7). Of the three diagnosed clinically, two were walking before 18 months and would have been missed by the programme. At present therefore 40% of the known cases have been detected by the programme, but this figure may well decrease if further cases are found in this cohort.

At the outset it was theoretically expected that at best 50% of cases would be detected, if even this figure cannot be achieved it makes the screening programme less worthwhile. If one of the main advantages of early diagnosis is secondary prevention, then the fewer cases picked up through the screening programme, the smaller the percentage of possibly preventable cases. It has been calculated that 15–20% of secondary cases can be prevented by newborn screening.[21] This figure falls to less than 10% if screening is performed at 18 months[9] assuming a 50% detection rate, and will be considerably less than 10% if the detection rate falls much below 50%. The impact for secondary prevention of a programme of the type described will therefore be small.

In our study out of a total of seven cases two would have been preventable by earlier diagnosis. Deletions of the dystrophin gene have been found in one of these families meaning that accurate antenatal diagnosis is available to them. In this family it was the detection of the younger boy through the screening programme that led to the older brother being diagnosed.

The reasons why less than 50% of cases were detected are that the uptake of developmental screening was low with only 79% of boys receiving a Denver developmental screening test; only 61% of the boys who were not walking had a creatine kinase assay and, lastly, three cases were diagnosed before 18 months. This is unusual and we believe that in one case the existence of the programme had heightened awareness of the condition leading to earlier diagnosis.

There were 335 boys who were not walking; of the boys that did not have a creatine kinase assay some may already have had alternative diagnoses and in some the parents may have declined the offer of a creatine kinase assay. The actual reason for the test not being done in individual cases was not recorded. The 205 boys that did have the assay may therefore be a selected group. There were no false positives with the assay, and though only 205 assays were carried out two cases were diagnosed. This ratio of one diagnosis in 100 tests is acceptable for a simple, cheap, assay for a serious condition. The creatine kinase assay is reliable and its use in screening for Duchenne muscular dystrophy has been reported in several studies.[22] [23] In Scheuerbrandts *et al*'s voluntary screening programme the false positive rate was only 0·065%.[23]

Three of the boys with Duchenne muscular dystrophy in this study are appreciably delayed developmentally, two are marginally delayed, and the other two are below average. Four of the boys also show delay in language development. It could therefore be argued that they would have been picked up anyway if all boys with developmental delay are investigated for Duchenne muscular dystrophy, assuming that developmental delay is recognised efficiently in the community.

The incidence of boys who were not walking (1·7%) is less than that reported by Neligan and Prudham[17] even though our criteria were less strict (4 independent steps as opposed to 10). This difference may be explained by the general trend for developmental abilities to improve,[24] [25] or it may reflect an under reporting of boys who were not walking on the computer returns. .

The logistic problems of this study were considerable. There were problems of acceptability both with parents of children with delayed walking and with their doctors. Despite considerable efforts many children missed the Denver screening test and of those who were not walking an appreciable number did not have a creatine kinase assay. We believe, therefore, that a formal screening programme such as ours for detecting Duchenne muscular dystrophy is probably not justified for the returns we achieved. Nevertheless we do believe that it is essential that creatine kinase assays are done as part of the assessment of developmental delay in all boys.

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# Treatment of Pseudomonas aeruginosa colonisation in cystic fibrosis

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SUMMARY To test whether early treatment could postpone the chronic colonisation of the respiratory tract with mucoid strains of *Pseudomonas aeruginosa* in patients with cystic fibrosis, we performed a pilot study in 28 patients aged 2 to 18 years. A two week course of azlocillin (150 mg/kg/day) and tobramycin (10 to 15 mg/kg/day) was given after a mean duration of *P aeruginosa* colonisation of five months (range one to 11 months). Weight for height increased significantly by 3·5% (SEM 0·7%) of the predicted normal after chemotherapy. The eradication of *P aeruginosa* that was achieved in 18 children directly after hospital treatment was only temporary. Samples from only 10 and five patients remained negative three and six months after treatment, respectively. Five children remained free from *P aeruginosa* for a prolonged period of 14 to 32 months.

We conclude that, apart from the clinical improvement in all patients, some children might benefit from early antipseudomonas treatment with respect to the bacteriological outcome. Most children, however, experience only a temporary reduction in colonisation. Further investigations in form of controlled clinical trials seem justified.

Pulmonary infection is the primary cause of morbidity in patients with cystic fibrosis. *Pseudomonas aeruginosa* acts as the main bacterial pathogen that causes a persisting lung infection.[1] The *P aeruginosa* strains are usually of the mucoid, alginate producing variant, whose presence is usually a diagnostic feature of the disease.[2] The chronic colonisation with mucoid *P aeruginosa* is associated with an appreciable clinical deterioration of the patient. This poses a serious therapeutic problem as the eradication of mucoid *P aeruginosa* from sputum by antibacterial chemotherapy is virtually impossible.[3]

Several reports suggest that the appearance of mucoid *P aeruginosa* in patients with cystic fibrosis is preceded by an asymptomatic period of colonisation of the upper respiratory tract with non-mucoid *P aeruginosa* strains.[4] A clinical trial with intravenous antipseudomonas treatment during the initial phase of *P aeruginosa* colonisation has not been reported.

Therefore we performed an open study to test the hypothesis as to whether early antipseudomonas treatment can eradicate *P aeruginosa* for a prolonged period of time, thereby postponing the chronic stage of *P aeruginosa* colonisation in patients with cystic fibrosis.

## Patients and methods

### PATIENTS

All patients with cystic fibrosis attending the cystic fibrosis outpatient centre at the Hanover Medical School were regularly examined for *P aeruginosa* in the respiratory tract. The patients were included in the study according to the following criteria: (a) primary growth of *P aeruginosa* in the sputum or deep throat swabs, (b) demonstration of a second *P aeruginosa* positive specimen four to eight weeks after the initial positive sample, and (c) treatment at our centre for at least 12 months before the initial demonstration of *P aeruginosa*. Out of the 34 patients who met these criteria since June 1983, six children were excluded either because they were below 2 years of age (n=3), they had pulmonary surgery (n=1), or there were parental objections (n=2).

### STUDY PROTOCOL

After the presence of *P aeruginosa* in sputum had been confirmed in a sample taken several weeks after the initial positive specimen, the patients were asked to attend for treatment at the hospital at their earliest convenience. Patients and their parents gave informed consent.

The treatment was initiated on the day of admission. The combination of an initial azlocillin injection (150 mg/kg/day) followed by a tobramycin infusion (10 mg/kg/day) for 30 minutes was given at eight hour intervals. The routine treatment consisted of a high energy diet with a normal fat content supplemented with enteric coated, acid resistant pancreatic enzymes (Kreon or Panzytrat) and vitamins, including vitamin E. Additionally, physiotherapy and aerosol treatment with normal saline and salbutamol was continued throughout the hospital stay. Twelve patients received continuous oral antistaphylococcal antibiotics in addition to the treatment mentioned above.

### LABORATORY AND CLINICAL INVESTIGATIONS

Before intravenous treatment venous blood samples were taken to determine the erythrocyte sedimentation rate, whole blood cell count, concentrations of immunoglobulins, serum creatinine, and urea, and the activities of liver enzymes. Trough and peak tobramycin serum concentrations were measured directly before and 30 minutes after terminating the sixth tobramycin infusion by using a fluorescence polarisation immunoassay (Abbott). The tobramycin dose was titrated to achieve peak serum concentrations between 6 and 12 mg/l.

Blood gases were analysed in arteriolar blood from the middle portion of the ear helix. Chest radiographs were taken if the last one had been performed more than six months ago. The condition of the chest was scored according to the classification of Chrispin and Norman[5] by a radiologist who had no clinical knowledge of the patient.

Lung function was measured in 16 children who were older than 6 years. A body plethysmograph (Fenyves and Gut) was used for the determination of the residual volume and airway resistance. Areas of air trappings were evaluated by the helium dilution technique and calculated as follows: (TGV-FRC)/TGV×100 (TGV: thoracic gas volume, FRC: functional residual capacity). To interpret the lung function results a comparison with the normal values obtained in our laboratory was made.[6] Results from uncooperative children without prior experience in lung function tests were excluded.

### BACTERIOLOGICAL EVALUATION

Specimens obtained from deep throat swabs or sputa were plated on selective media. Appropriate culture techniques were used to enhance the recovery of *P aeruginosa*, *Haemophilus influenzae*, and *Staphylococcus aureus*. The standard disc technique was used to test the susceptibility of the infective organisms to antibiotics. Secondary cultures of the *P aeruginosa* strains were either maintained on non-aerated agar slants at room temperature or stored at −70°C until use. Serotyping of *P aeruginosa* strains was done by agglutination tests with commercial antisera (Pasteur Diagnostika).[7] The phage typing pattern was assessed with the routine set of 20 bacteriophages.[8] Pyocin typing was carried out by the spotting method.[9] Strains were classified as different if they differed by serotype, and/or by at least one response to a pyocin indicator strain, and/or at least two responses to phages. Analyses were performed on *P aeruginosa* strains obtained before the children were admitted to hospital, on the day of hospital admission, and during the six months after the throat swab had again become positive.

## Results

Twenty eight children and adolescents with cystic fibrosis participated in the study. When admitted to the hospital the mean age was 9·0 years (range 2 to 18 years), whereas the mean age at initial *P aeruginosa* colonisation was 8·6 years.

### PRELIMINARY CLINICAL FINDINGS

The clinical state of the patients at the beginning of treatment is listed in table 1. Most children showed a mild to moderate degree of the disease, in which the mean values for weight, lung function tests, and oxygen pressure were in the normal range or slightly lower. Although most patients were clinically

Table 1 *Clinical data and lung function test results of patients at the beginning of antipseudomonal chemotherapy*

| | *No of children* | *Mean* | *Range* |
|---|---|---|---|
| Age (years) | 28 | 9·0 | 2– 18 |
| Weight for height* | 28 | 93·7 | 71–136 |
| Chrispin-Norman score† | 19 | 8·8 | 2– 23 |
| Oxygen pressure (kPa) | 22 | 10·5 | 5·1–13·1 |
| IgG (g/l) | 17 | 12·5 | 5– 23 |
| Vital capacity* | 10 | 88·4 | 49–131 |
| Functional residual capacity* | 12 | 132·7 | 92–181 |
| Functional residual capacity/total | 10 | 0·541 | 0·42–0·74 |
| Trapped gas† | 13 | 32·4 | 16– 53 |
| Airway resistance* | 13 | 115·9 | 31–288 |

*% Of normal predicted; †(TGV-FRC)/TGV×100; FRC=functional residual capacity, TGV=thoracic gas volume.

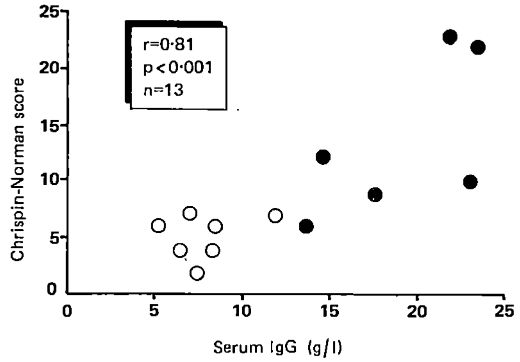

Fig 1 *Association between serum IgG concentrations and Chrispin-Norman scores at the beginning of treatment. The patients were grouped according to the subsequent type of P aeruginosa colonisation:* ○ *denotes intermittent,* ● *chronic.*

asymptomatic, three children had already experienced considerable pulmonary deterioration before the acquisition of *P aeruginosa.*

A linear correlation between IgG concentrations and lung involvement, expressed as the Chrispin-Norman score, was found (r=0·81, p<0·001 in 13 children) (fig 1).

BACTERIOLOGICAL FINDINGS BEFORE TREATMENT

The association of the onset of pseudomonas colonisation to treatment is shown in fig 2. Fourteen and 20 children were infected for the first time during the preceding four and six months, respectively. Most patients harboured rough *P aeruginosa* strains, but in eight patients mucoid *P aeruginosa* strains were isolated at the time of admission, and in two patients mucoid variants had already been present in the initial positive specimen.

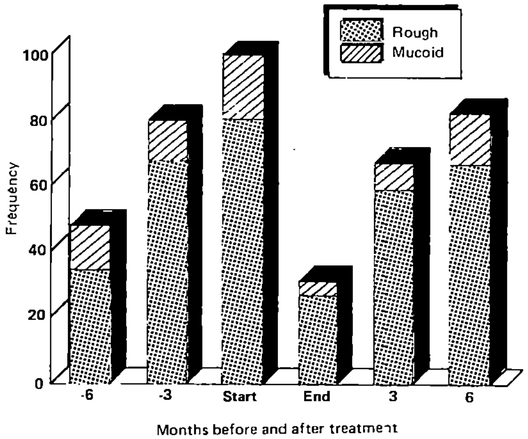

Fig 2 *Frequency of P aeruginosa (rough or mucoid) in throat swabs or sputa before and after antimicrobial treatment.*

Additional bacteria were isolated in 21 of the 28 patients at the beginning of the antipseudomonas treatment (table 2).

*S aureus* was the most frequent pathogen, followed by *Enterobacter cloacae, Escherichia coli, Proteus mirabilis, Klebsiella pneumonia,* and *H influenzae.* Out of the seven patients who did not harbour any other pathogens besides *P aeruginosa,* five were on continuous oral antibiotics. Only seven of the 21 patients with multiple bacterial isolations had received such treatment.

CLINICAL RESULTS

Chemotherapy led to a significant increase in mean (SEM) body weight of 1·7 (0·3) kg after two weeks of hospital treatment. Percentage ideal weight for height increased from an initial mean (SD) 93·7 (12·4) to 97·2 (13·4) after treatment (mean (SEM) difference: 3·5 (0·7)% of ideal body weight, p<0·001). The corresponding SD scores were −0·61 before and −0·34 after treatment, respectively. The weight gain persisted for six months after the termination of treatment (fig 3). No significant improvements in lung function tests were found in the 10 children repeatedly tested. This may be due to the lack of severe abnormalities at the initiation of treatment. Indices of inflammation, which had been normal in most patients at the beginning of treatment, remained unchanged after antipseudomonas treatment.

SIDE EFFECTS

In general the treatment was well tolerated. All children received the complete two week course of

Table 2 *Results of bacteriological examination of throat swabs or sputum taken before and after a two week course of antipseudomonal chemotherapy. Results are No of patients*

| | *Before chemotherapy* | *After chemotherapy* |
|---|---|---|
| *P aeruginosa* (all strains) | 28 | 10 |
| Mucoid *P aeruginosa* | 8 | 1 |
| *Staphylococcus aureus* | 7 | 1 |
| *Enterobacter cloacae* | 4 | 0 |
| *Escherichia coli* | 2 | 2 |
| *Haemophilus influenzae* | 1 | 1 |
| Others | 4 | 1 |
| Two or more different bacteria | 3 | 0 |
| *Candida albicans* | 6 | 16 |

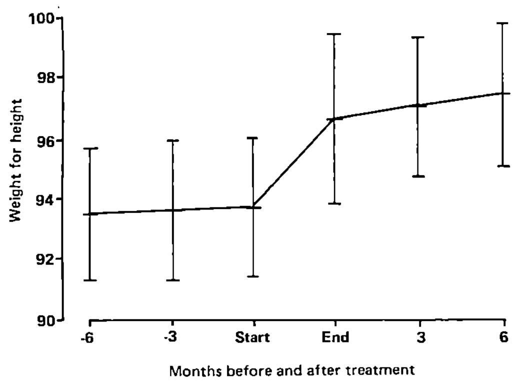

Fig 3 *Weight for height expressed as the percentage of the predicted normal before and after antipseudomonal treatment. Results are mean (SEM).*

Table 3 *Total hospital admissions including the initial course of antimicrobial chemotherapy*

| *No of intravenous courses* | *No of children* | *P aeruginosa colonisation* |  | *Aerosol treatment* |
|---|---|---|---|---|
|  |  | *Intermittent* | *Chronic* |  |
| 1 | 14 | 7 | 6* | — |
| 2 | 7 | 3 | 4 | 3 |
| 3 | 5 | — | 5 | 5 |
| 4 | 2 | — | 2 | 1 |

The patients were classified according to the bacteriological results from throat swabs and sputa during the follow up period. Intermittent colonisation was defined as having less than 50% *P aeruginosa* positive specimens. The five children who were free of *P aeruginosa* for a prolonged period were included in this group. Chronic colonisation was defined as having more than 50% *P aeruginosa* positive specimens.

*One patient was excluded from this analysis because of only an eight month follow up.

antimicrobials. Side effects were seen infrequently. Nevertheless, four children developed a skin rash after 10 days of treatment, with concomitant fever in two patients. After drug discontinuation, rash and fever subsided. No signs of drug induced nephrotoxicity or ototoxicity were found after treatment. Serum creatinine values did not increase compared with baseline values (57·6 μmol/l before compared with 55·6 μmol/l after treatment), and hearing tests gave no abnormal results.

### BACTERIOLOGICAL RESULTS

Eighteen children were free of *P aeruginosa* two days after treatment, and other bacteria were found in only five patients. Azlocillin resistance developed in two patients after treatment. Candida species were isolated from samples of 16 patients after treatment, however, compared with only six before (table 2).

The eradication of *P aeruginosa* that was achieved in 18 patients directly after hospital treatment was only temporary. Three and six months after treatment, samples from only 10 and five children, respectively, remained negative. Recolonisation with *P aeruginosa* was observed in four of the five patients after a lag period of 14, 20, 24, and 32 months after treatment. The patient with persistently negative sputa has been observed for 15 months after treatment until the present.

### LONG TERM FOLLOW UP

The overall outcome of the 28 children including the last visit to the clinic is shown in table 3. Fourteen children needed additional antipseudomonas treatment due to pulmonary exacerbations, inadequate weight gain or weight loss, decline of pulmonary function, or persistent signs of inflammation. Five of the 14 children received two additional treatments, and two children three additional treatment courses. This resulted in a total of 37 courses of intravenous antimicrobial treatment during a total of 370 months of follow up time—that is, 1·2 treatments per patient per year.

A group of nine patients received aminoglycoside inhalation treatment that consisted of 80 mg tobramycin twice daily after physiotherapy during the follow up period, usually starting after the second course of intravenous chemotherapy.

### *P AERUGINOSA* TYPING

Before the children were admitted to hospital a total of 57 different *P aeruginosa* strains were isolated, indicating that most patients harboured two or more different *P aeruginosa* strains in their respiratory tract. This was in contrast with the first positive throat swab after chemotherapy that showed only one *P aeruginosa* strain in most cases. Serotyping, phagetyping, and pyocintyping showed that 17 patients had acquired novel strains, eight patients were harbouring the same set of strains as before antipseudomonal treatment, and two patients were infected with a mixed population of old and new strains.

### RISK FACTORS FOR CHRONIC *P AERUGINOSA* COLONISATION

In an attempt to define the risk factors of chronic *P aeruginosa* colonisation, the patients were divided into two groups according to the incidence of *P aeruginosa* positive throat swabs obtained at clinic visits during the years after initial antipseudomonas treatment.

Table 4 *Mean clinical and laboratory data at the time of hospital admission classified according to P aeruginosa colonisation*

| | *P aeruginosa colonisation* | | *p Value* |
|---|---|---|---|
| | *Intermittent (n=10)* | *Chronic (n=17)* | |
| Age (years) | 8·2 | 9·8 | 0·370 |
| Duration of colonisation (months) | 4·9 | 5·2 | 0·717 |
| Weight for height (%) | 96·7 | 93·3 | 0·561 |
| Vital capacity (%) | 79·3 | 94·5 | 0·304 |
| Functional residual capacity/total lung capacity | 0·548 | 0·537 | 0·856 |
| Oxygen pressure (kPa) | 11·3 | 10·0 | 0·09 |
| Chrispin-Norman score | 5·1 | 11·5 | 0·01 |
| IgG (g/l) | 8·2 | 16·4 | 0·002 |
| Serum urea (mmol/l) | 5·2 | 3·7 | 0·024 |

For definition of the colonisation groups refer to table 3.

Table 5 *Frequencies of pathogens other than P aeruginosa in a total of 204 throat swabs or sputa obtained at clinic visits during the two years before hospital admission grouped by outcome of P aeruginosa colonisation. Results are No of specimens (% of each group)*

| *Time before treatment (months)* | *Pathogens not found* | *Gram positive bacteria* | *Gram negative bacteria* | *Yeasts* |
|---|---|---|---|---|
| 24–12 | | | | |
| *P aeruginosa* colonisation: | | | | |
| Intermittent (n=34) | 19 (56) | 3 (9) | 10 (30) | 2 (6) |
| Chronic (n=65) | 40 (61) | 6 (9) | 11 (18) | 8 (12) |
| 12–1 | | | | |
| *P aeruginosa* colonisation: | | | | |
| Intermittent (n=38) | 18 (47) | 6 (17) | 7 (18) | 7 (18) |
| Chronic (n=67) | 27 (40) | 9 (14) | 23 (34) | 8 (12) |

Table 4 compares clinical and laboratory results obtained at the beginning of the first intravenous treatment of the two groups of patients. Children who subsequently developed intermittent colonisations were observed compared with patients with chronic *P aeruginosa* colonisations. Surprisingly, there were no differences in age or in duration of *P aeruginosa* colonisation before treatment, nor in weight for height or lung function. However, the chest radiograph was significantly worse in the group which later became chronically infected. In addition, high initial serum IgG concentrations and low serum urea concentrations were associated with chronic *P aeruginosa* colonisation.

Table 5 shows the incidence of bacteria apart from *P aeruginosa* during a period of two years before the children were admitted to hospital. During the first period (24 to 12 months before treatment) no throat swab yielded *P aeruginosa*, but other Gram negative species were isolated in 21 and Gram positive bacteria in nine of 99 specimens. The frequency of bacterial isolations increased to 43% during the year before treatment. The frequency of additional bacteria before antipseudomonas treatment did not differ in the two patient groups.

## Discussion

In the present study intravenous antipseudomonal treatment was given early with respect to the current treatment schedules for *P aeruginosa* colonisation as an attempt to eliminate the bacteria from the respiratory tract, thereby trying to postpone the chronic phase of *P aeruginosa* colonisation. The results, however, show that the permanent eradication of *P aeruginosa* from sputum is very difficult to achieve in most patients, even if only a few months have elapsed since the first detection of *P aeruginosa*. Although bacterial typing indicates that the initial *P aeruginosa* strain can be successfully eliminated by antimicrobial treatment, other *P aeruginosa* strains will subsequently take residence in the respiratory tract, because the compromised host with cystic fibrosis remains susceptible to recolonisation with *P aeruginosa*.

Raised serum IgG concentrations as well as the severity of chest involvement, measured by the Chrispin-Norman radiological score, were identified as risk factors for chronic *P aeruginosa* colonisation. This suggests that host factors play an important role in the progression of colonisation.

In patients without cystic fibrosis, pseudomonas colonisation is seen only after injury to the respiratory mucosa has occurred—for example, during endotracheal intubation or in patients with tracheostomy or chronic bronchiectases. The initial step of bacterial colonisation is the adherence of the organism to the cells of the mucosal surface.[10] Woods *et al* identified the loss of fibronectin from cell surfaces as a promoting factor for the initial epithelial damage in cystic fibrosis.[11] Investigations performed in our department with buccal cells from patients with cystic fibrosis showed that *P aeruginosa* can attach more easily to cells from chronically infected patients with cystic fibrosis than to cells obtained from these patients without bacterial colonisation.[12] In addition, there was a positive correlation between the duration of *P aeruginosa* colonisation and the adherence of *P aeruginosa* strains to buccal epithelial cells.

The fact that 60% of our patients grew Gram positive or Gram negative bacteria in addition to *P aeruginosa* in the year before initiation of treatment indicates that *P aeruginosa* is only one of several different bacterial species invading the respiratory tract. On the other hand, this finding could also mean that the mucosal damage caused by certain bacteria contributes to the subsequent binding of *P aeruginosa*.

After bacteria have successfully adhered to the mucosa or mucins of the respiratory tract the organisms start to replicate, release toxins, and finally, induce mucosal damage. In the current study, patients who later become chronically infected with *P aeruginosa* showed a more severe degree of lung involvement on initial chest radiographs compared with patients with only intermittent colonisations. If it is assumed that higher radiological scores are caused at least in part by defective endobronchial clearance mechanisms, these results show that the importance of impaired mucociliary clearance for the persistent growth of *P aeruginosa* should not be underestimated.

The bacteriological results obtained from the current study were in agreement with those reported by other authors.[13] Two thirds of the patients were free of *P aeruginosa* after a two weeks course ot antipseudomonas treatment. An encouraging finding was the absence of *P aeruginosa* in the respiratory tract of five children over prolonged periods of 14 to 32 months. Whether this is due to antimicrobial treatment or rather to specific host factors remains unclear, as no control group was investigated in the present study.

The clinical benefit of the treatment was shown by a significant increase in weight for height, which persisted during the six months after chemotherapy. It must be emphasised, however, that antibiotics eliminated other Gram negative and Gram positive bacteria in addition to *P aeruginosa*. The weight gain may therefore not only be attributed to the decrease of *P aeruginosa* colonisation, but to a more generalised antimicrobial action. Furthermore, hospital treatment in itself may improve symptoms and well being in cystic fibrosis patients.[14 15] This could be because the whole treatment programme, including physiotherapy, can be performed on a regular basis, which is not always possible at home.

If recolonisation with *P aeruginosa* occurs after antimicrobial treatment, the question arises whether or not repeated courses of antimicrobials should be given at regular intervals, as proposed by Szaff *et al.*[13] The Danish group reported stable pulmonary function data during the first five years of colonisation with *P aeruginosa*, if the patients were treated every three to four months, whereas a historical control group showed a decline in peak expiratory flow during the same period. The major drawbacks of this kind of treatment are the interference with the patients' social life and the high costs of treatment. Inhalation of aerosolised antibiotics for months and years on an ambulatory basis has been proposed as an alternative approach for adult patients with cystic fibrosis and chronic *P aeruginosa* colonisation.[16] No data are available concerning the optimal onset of aerosol treatment, however, and the question as to which patients will benefit most has not been resolved.

In conclusion, from the results of the present pilot study early treatment of *P aeruginosa* colonisation appears to be a reasonable approach in patients with cystic fibrosis. A temporary reduction in colonisation can be achieved in most children. As the patients remain susceptible to recolonisation, however, only few patients will benefit from an improved prognosis due to a prolonged *P aeruginosa* free interval. Prospective randomised studies are needed to investigate the value of early antibiotic treatment in patients with newly detected *P aeruginosa* colonisation. Moreover, the role of host factors for the development of chronic *P aeruginosa* colonisation should be studied in more detail.

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# Anterior abdominal wall defects

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SUMMARY A total of 48 infants with abdominal wall defects referred to the South West Regional Neonatal Surgical Centre over a period of six years were reviewed. There were 27 (56%) infants with gastroschisis and 21 (44%) infants with exomphalos. At the regional centre, four pregnancies with gastroschisis were terminated following a prenatal diagnosis, one child was stillborn, and one with exomphalos and trisomy 13 died soon after birth. Of the remaining 42 live births, the one year survival for babies born with a gastroschisis was 95% (21/22) and with an exomphalos was 81% (17/20). All deaths, except one, were due to factors other than the abdominal defect. The effect on outcome of prenatal diagnosis, parental counselling, in utero transfer, mode of delivery, and methods of surgical closure was reviewed.

The management of infants with gastroschisis or exomphalos presents problems to neonatologists, paediatric surgeons, and obstetricians. Since their recognition in the early 1960s as distinct entities there has been a progressive improvement in survival.[1 2] With the more frequent ultrasonographic diagnosis of these defects, knowledge of the long term outlook is of utmost importance when conselling parents on the question of termination. If the pregnancy continues, the place, time, and mode of delivery need to be planned and the postnatal management discussed with the parents.

## Patients and methods

Obstetric, paediatric, and ultrasound records were reviewed for all 48 infants with abdominal wall defects referred to the South West Regional Neonatal Surgical Centre during the period 1981 to 1986 inclusive. Follow up on all surviving infants was for between one and six years. Precise termination statistics were only available for the Bristol Maternity Hospital.

## Results

Six of the 48 cases originally booked for antenatal care at the Bristol Maternity Hospital. All received prenatal ultrasonography and the diagnosis of an abdominal wall defect was made in five (83%) (mean gestational age 17·8 weeks, range 17–19). Four of these mothers subsequently elected for termination of pregnancy; all four fetuses had the gastroschisis defect. The remaining infant with an in utero diagnosis of gastroschisis died as an unexpected stillbirth at 37 weeks. The sixth child, with trisomy 13 and exomphalos, which was not detected antenatally, died soon after birth without active treatment being offered.

Of the remaining 42 live births who originally booked for antenatal care in district general hospitals outside Bristol, 26 (61%) had recorded evidence of prenatal ultrasonography and the diagnosis of anterior abdominal wall defect was made in nine (34·6%) (mean gestational age 20·7 weeks, range 12–35). Details of the prenatal ultrasound studies are shown in table 1. Subsequently six children in

Table 1 *Details of prenatal ultrasound*

| | *No of infants* | *No (%) with ultrasonography recorded* | *No (%) with positive scan* | *Detection rate (No (%) of total)* | *Mean (range) gestational age (weeks)* |
|---|---|---|---|---|---|
| Total | 48 | 32 (66) | 14 (43) | 14 (29) | 22·6 (16–36) |
| Booked at: | | | | | |
| Bristol | 6 | 6 (100) | 5 (83) | 5 (83) | 17·8 (17–19) |
| District general hospital | 42 | 26 (62) | 9 (34) | 9 (21) | 20·7 (12–35) |

Table 2 *Comparative perinatal data*

| | *Gastroschisis (n=27)* | *Exomphalos (n=21)* |
|---|---|---|
| Maternal age (years) | 22·6 | 26·5 |
| Parity (No (%)) | | |
| Primipara | 19 (70) | 9 (42) |
| Multipara | 8 (29) | 12 (58) |
| Mean (range) gestational age (weeks) | 37·2 (33·5–40·0) | 36·8 (30·0–40·0) |
| Mean (range) birth weight (g) | 2400 (1460–3520) | 2800 (1590–4140) |
| Mean (range) Apgar score at 5 minutes | 8·3 (10·0–4·0) | 8·6 (4·0–10·0) |
| Mean (range) serum albumin (g/l) | 26·4 (21·0–37·0) | 28·0 (20·0–35·0) |
| Delivery (No (%))* | | |
| Vaginal | 14 (61) | 15 (72) |
| Caesarean | 7 (30) | 6 (28) |
| Forceps | 2 (9) | |
| Surgical treatment (No (%))† | | |
| Primary closure | 12 (55) | 9 (45) |
| Delayed/silo (gastroschisis) or serial (exomphalos) | 10 (45) | 11 (55) |
| Mean (range) weight (kg)† | | |
| At 6 months | 5·9 (3·8–8·5) | 6·6 (4·2–8·1) |
| At 1 year | 8·1 (5·8–10·3) | 9·4 (7·2–11·1) |
| Survival (No (%))† | | |
| At 6 months | 21 (95) | 18 (86) |
| At 1 year | 21 (95) | 17 (81) |

*For gastroschisis n=23 as four pregnancies were terminated. †For gastroschisis n=22 as one infant was stillborn; for exomphalos n=20 as one infant died soon after birth.

Table 3 *Associated anomalies in anterior abdominal wall defects, Bristol 1981–6*

| | *Gastroschisis* | *Exomphalos* |
|---|---|---|
| **Cardiac:** | | |
| Total anomalous pulmonary venous drainage | 0 | 1 |
| Pulmonary artery hypoplasia | 0 | 2 |
| Major septal defects | 0 | 1 |
| Patent ductus arteriosus | 2 | 2 |
| Persistent fetal circulation | 0 | 1 |
| Total (%) | 2 (9) | 7 (33) |
| **Gastrointestinal:** | | |
| Persistent vitellointestinal duct | 1 | 1 |
| Meckel's diverticulum | 0 | 1 |
| Ileal atresia | 1 | 1 |
| Morgagni defect | 0 | 1 |
| Rectal atresia | 1 | — |
| Colonic atresia | 1 | — |
| Total (%) | 4 (18) | 4 (20) |
| **Other:** | | |
| Undescended testis | 2 | 0 |
| Hemihypertrophy | 1 | 0 |
| Lissencephaly | 1 | 0 |
| Congenital dislocated hip | 1 | 1 |
| Hypospadias | 0 | 1 |
| Beckwith's syndrome | 0 | 5 |
| Cystic kidney | 0 | 1 |
| Trisomy 13 | 0 | 1 |
| Total (%) | 5 (23) | 9 (45) |

this group were transferred in utero to the regional centre and all survived; the remaining three were transferred after birth, with one death resulting from problems in transit.

Comparative perinatal data for the two groups are shown in table 2.

### GASTROSCHISIS

No major cardiac anomalies were found in the 22 liveborn infants in this group, though two had a symptomatic patent ductus arteriosus. Fetal pathological examination in five cases (four terminations and one stillbirth) showed no major cardiac anomaly. Four infants (18%), however, had associated gastrointestinal anomalies, all amenable to corrective surgery (see table 3). The well documented motility and malabsorption problems associated with gastroschisis[3] were reflected in the median nude weights at 6 months and 1 year of age, which were at or below the 3rd centile. Survival in this group was excellent at 95% at 1 year of age, the only death being the one attributable to problems in transfer (table 2).

### EXOMPHALOS

By comparison the group of infants with exomphalos provided more troublesome management problems. Of 20 infants only nine (45%) were amenable to primary closure; prosthetic Dexon sheets were used in five of these infants.

Associated cardiac anomalies were found in seven (33%) infants with exomphalos, although none of these defects were detected prenatally. Three of the four deaths in the group with exomphalos were due to major cardiac defects in the children who received prenatal ultrasonography (mean gestational age 17 weeks) without detection of either exomphalos or cardiac anomaly.

In four (20%) of infants with exomphalos there were associated gastrointestinal anomalies that did not directly affect the mortality (see table 3).

Survival rates in this group were 86% at 6 months and 81% at 1 year of age; only one child died as a direct result of the abdominal defect—from fulminating septicaemia associated with the use of a prosthetic silo sac. In contrast with the group with gastroschisis the median nude weights at 6 months and 1 year of age were at or above the 10th centile (table 2).

## Discussion

With a recorded incidence of 1:2550 pregnancies children with anterior abdominal wall defects are not an uncommon management problem, especially in regional referral centres.[4] A vast improvement in survival statistics since the early 1960s has been attributable to improved neonatal intensive care overall[5]; in this series it is over 80% at one year.

We report a prenatal detection rate of only 29% overall in our series. The percentage of positive scans in the regional centre and district general hospitals were 83% and 34% respectively ($p<0{\cdot}01$). One major value of prenatal ultrasound detection of abdominal wall defects is that it may allow thorough investigation for the presence of cardiac or chromosomal abnormalities in fetuses with exomphalos. None of the associated major cardiac defects were diagnosed antenatally, however, and these were responsible for three of the four deaths in the group with exomphalos. The outlook for infants with exomphalos without these associated abnormalities, and for all infants with gastroschisis, is very good in terms of survival and development; thus in future parents may be less likely to opt for termination of pregnancy. Such infants should be delivered at a regional centre whenever possible to avoid the problems of postnatal transfer. The mode and timing of delivery should be determined by obstetric indications. In this series there appears to be no advantages in elective caesarean section for infants with gastroschisis or exomphalos; however, a prospective randomised trial is necessary. Wherever possible primary closure of the defect should be the rule, using prosthetic inlay grafts and primary skin cover as a suitable alternative. Should postnatal transfer be necessary it is suggested the infant be stabilised before transfer to the regional centre.

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# Cereal based oral rehydration solutions

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SUMMARY A total of 257 boys (age range 4–55 months), who had acute diarrhoea with moderate to severe dehydration, were randomly assigned to treatment with either the World Health Organisation/United Nations Childrens Fund (WHO/Unicef) recommended oral rehydration solution or cereal based oral rehydration solution made either of maize, millet, sorghum, or rice. After the initial rehydration was achieved patients were offered traditional weaning foods. Treatment with oral rehydration solution continued until diarrhoea stopped. Accurate intake and output was maintained throughout the study period. Efficacy of the treatment was compared between the different treatment groups in terms of intake of the solution, stool output, duration of diarrhoea after admission, and weight gain after 24, 48, and 72 hours, and after resolution of diarrhoea. Results suggest that all the cereal based solutions were as effective as glucose based standard oral rehydration solution in the treatment of diarrhoea.

Diarrhoea and its interaction with malnutrition is an important health problem and a major cause of death in infants and young children throughout the non-industrialised world. In these countries children under 5 years may suffer two to five diarrhoeal episodes resulting in considerable illness for 20–30 days each year (R E Black, *et al,* unpublished observations).[1–5] About one in every 10 children born in these countries dies from diarrhoea before reaching the age of 5 years.[6] It is reported that in Africa, Asia, and Latin America alone 750–1000 million cases occur in children under 5 years annually.[7]

Effective and timely use of oral rehydration therapy has been shown to reduce the diarrhoea related mortality. One way of increasing the coverage of oral rehydration therapy is to ensure its availability and accessibility to every household in areas where diarrhoea is endemic. Knowledge of how to administer oral rehydration therapy at the earliest onset of diarrhoea is also vital. World Health Organisation/United Nations Children's Fund (WHO/Unicef) recommended oral rehydration solution has not been readily available in many countries because of cost and logistic problems in procurement and distribution. This is especially the case in many African countries. The use of packets of WHO/Unicef oral rehydration solution should not be the only strategy for reducing diarrhoea related mortality. Therefore we compared the efficacy of oral rehydration solutions made from various low cost cereals readily available and accessible in most parts of Africa.

## Patients and methods

The study was conducted in the paediatric ward of Kakamega Provincial General Hospital by staff experienced in conducting balance studies in children with diarrhoea. The research proposal was approved by the Scientific and Ethical Review Committees of the Kenya Medical Research Institute and the International Centre for Diarrhoeal Disease Research in Bangladesh (ICDDR, B). Boys aged 4–59 months with a history of three days or less of diarrhoea, judged to have moderate to severe degree of dehydration according to WHO criteria,[8] and without a history of prior medication were selected for the study.

Patients with a history of bloody diarrhoea, severe malnutrition, or signs of any systemic illness (except malaria) were excluded from the study. Informed consent was obtained from the parents or legal guardians of the patients before being included in the study.

No antibiotics were prescribed. Those needing antibiotics on clinical indications were taken out of the study. Once included in the study the patients were assigned to the different treatment groups after block randomisation.[9]

Packets of maize, millet, sorghum, and rice oral rehydration solutions were made up with 60 g of the respective cereals replacing the 20 g of glucose contained in the WHO/Unicef solution. The 60 g of cereal flour was boiled in 1100 ml of water for approximately 6–7 minutes and stirred continuously. The solution was brought to room temperature and electrolytes (sodium chloride 3·5 g, sodium bicarbonate 2·5 g, and potassium chloride 1·5 g) were added before administration.

### TREATMENT

Children in the control group received standard WHO/Unicef oral rehydration solution (sodium chloride 3·5 g, trisodium citrate dihydrate 2·9 g, potassium chloride 1·5 g, glucose 20 g, and water 1·0 l) and those in the study groups received cereal based solutions. Patients with severe dehydration received initial rehydration standardised for duration and volume by kg body weight through the intravenous route by half strength Darrow's solution.[10] After the initial rehydration of the severely dehydrated patients they were started on oral rehydration. Mothers were trained to feed oral rehydration solution to their children under supervision of research nurses and physicians. Accurate records (±1 g and ±1 ml) of intake of the solution, water, or any other food or fluid during the study period were maintained. Stool, urine, and vomit were collected separately and measured at intervals of eight hours. Patients were allowed plain water on demand. After the initial rehydration (six to eight hours) breast feeding and the foods usually fed to the child were continued and offered freely.

Efficacy was measured by assessing the volume of intake of the solution, stool volume, weight gain, and duration of diarrhoea after admission.

### LABORATORY TESTS

The stool and urine were examined microscopically on admission. Stool and rectal swabs were cultured for *Vibrio cholerae*, rotavirus, salmonella, shigella, and *Escherichia coli* groups. Routine investigations were carried out for clinical care of the patients and included total white blood count, haemoglobin concentration, haematocrit, malaria parasites, and concentrations of serum electrolytes. Body weight was measured on admission and after 24, 48, and 72 hours, and at discharge.

### STATISTICAL ANALYSIS

Statistical analyses were based on analysis of variance. Basically comparisons were made between individual cereal based and the WHO/Unicef glucose oral rehydration solutions on the rate of purging, change in body weight, urine output, vomit, solution intake, and duration of diarrhoea after admission.

Table 1 *Clinical features of children on different oral rehydration solutions on admission*

| *Admission variables* | *Treatment groups* | | | | |
|---|---|---|---|---|---|
| | *Maize (n=51)** | *Sorghum (n=48)** | *Rice (n=51)** | *Millet (n=50)** | *Glucose† (n=50)** |
| Mean (SD) age (months) | 12 (6) | 13 (9) | 10 (5) | 11 (6) | 11 (8) |
| No (%) vomiting before admission | 50 (98) | 47 (98) | 48 (94) | 50 (100) | 46 (92) |
| Mean (SD) diarrhoea duration before admission (hours) | 64 (5·6) | 63 (6·5) | 70 (5·7) | 67 (5·7) | 69 (4·4) |
| Mean (SD) body weight at admission (kg) | 8 (1) | 8 (2) | 8 (2) | 8 (2) | 8 (2) |
| No (%) with moderate dehydration | 48 (94) | 43 (90) | 46 (90) | 39 (78) | 41 (82) |
| No (%) with severe dehydration | 3 (6) | 5 (10) | 5 (10) | 11 (22) | 9 (18) |
| Mean (SD) diarrhoea duration after admission (hours) | 45 (21) | 50 (20) | 42 (10) | 51 (11) | 46 (9) |
| No (%) treatment failures | 1 (2) | 3 (6) | 1 (2) | 1 (2) | 1 (2) |

*Denotes successfully rehydrated cases only.
†WHO/Unicef recommended solution.

Table 2 *Fluid balance at the end of 24 hours treatment. Results are mean (SD)*

| *Type of oral rehydration solution* | *Intake in ml/kg body weight* | | | *Output in ml/kg body weight* | | | |
|---|---|---|---|---|---|---|---|
| | *Oral rehydration solution* | *Plain water* | *Total intake* | *Stool* | *Urine* | *Vomit* | *Total output* |
| Maize | 201 (29) | 37 (11) | 241 (33) | 83 (22) | 66 (15) | 28 (8)‡ | 178 (21) |
| Sorghum | 177 (24)† | 48 (16) | 229 (29) | 87 (27) | 58 (14) | 25 (6)§ | 169 (17) |
| Rice | 196 (23) | 38 (8) | 243 (33) | 100 (28) | 60 (16) | 19 (4) | 172 (21) |
| Millet | 200 (26) | 40 (10) | 240 (41) | 102 (30) | 68 (18) | 18 (5) | 179 (27) |
| Glucose* | 214 (31) | 39 (8) | 258 (57) | 103 (31) | 62 (12) | 16 (3) | 173 (23) |

*WHO/Unicef recommended solution.
†0·02<p<·0·05; ‡0·02<p<0·05; §0·04<p<0·05.

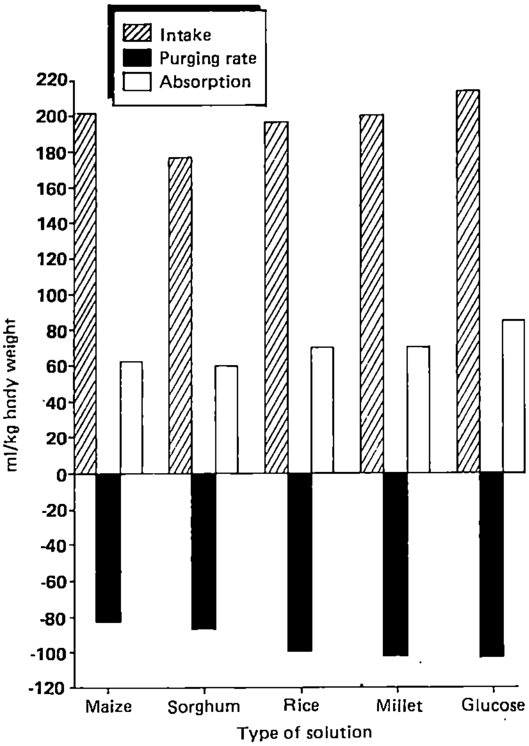

Figure *Fluid balance at the end of 24 hours.*

## Results

Clinical information relating to the study patients is presented in table 1. There were no significant differences between the individual treatment groups of cereal based and WHO/Unicef glucose solutions with regard to any of the clinical features. The mean (SD) ages of patients in each treatment group were similar 10 (0·8) to 13 (1·3) months. The five groups were also comparable with respect to mean duration of diarrhoea before admission, degree of dehydration, admission body weight, and mean duration of diarrhoea. After admission of the 257 patients recruited into the study, 250 (97%) were successfully rehydrated. No adverse reactions or complications were noticed in any of the treatment groups. The main cause of failure and subsequent removal from the study of these seven patients was due to persistent refusal to take the oral rehydration solution and subsequent negative fluid balance as indicated by continued loss of weight and concomitant worsening of dehyration. Preadmission vomiting was reported in 92–100% of the patients. There were no significant differences in the amount of oral rehydration solution, plain water, and total intake among any of the groups at the end of the first 24 hours of therapy (table 2 and figure). Full rehydration was achieved during the first 24 hours of treatment. Stool output or purging rates and urine output were also comparable in all the five groups.

Table 3 *Percent body weight gain by 24 hour periods in different oral rehydration solutions. Results are mean (SD)*

| *Type of oral rehydration solution* | *No* | *24 Hours* | *No* | *48 Hours* | *No* | *72 Hours* | *No* | *Discharge* |
|---|---|---|---|---|---|---|---|---|
| Maize | 51 | 6·5 (3·2) | 42 | 7·2 (4·3) | 29 | 7·1 (4·8) | 51 | 7·3 (4·1) |
| Sorghum | 48 | 4·7 (1·8) | 36 | 5·6 (2·0) | 21 | 6·8 (2·7) | 48 | 5·1 (1·5) |
| Rice | 51 | 6·0 (2·3) | 48 | 6·4 (1·2) | 34 | 6·2 (1·6) | 51 | 6·0 (3·1) |
| Millet | 50 | 5·8 (3·1) | 43 | 6·3 (2·9) | 26 | 5·3 (1·1) | 50 | 6·1 (2·4) |
| Glucose* | 50 | 6·9 (1·7) | 48 | 7·8 (2·1) | 28 | 7·3 (2·0) | 50 | 7·4 (3·2) |

*WHO/Unicef recommended solution.

The group receiving the maize based solution had a lower stool output than the control group receiving WHO/Unicef glucose based solution, but this difference was not significant. Vomit of 28 (8) ml and 25 (6) ml in the groups receiving the maize and sorghum based solutions respectively were each significantly higher than that found in the control group (16 (3) ml, $p<0\cdot05$). There were no differences in absorption of the oral rehydration solution per kg body weight between the treatment groups (figure).

All treatment groups and the control group showed similar weight gain compared with admission weight after 24, 48, and 72 hours of hospitalisation and at the resolution of diarrhoea (table 3).

## Discussion

After reports of successful trials of rice based oral rehydration solutions in Asia,[11–14] the Kenya Medical Research Institute decided to test some of the cereals that are widely available in Africa. Apart from a pilot study by Kinoti *et al* on a maize based solution,[15] we believe that this is the first study to assess the efficacy of different cereal based solutions in the management of acute childhood diarrhoea.

We attempted to follow recommended clinical practice by offering food with the solutions after the initial rehydration as oral rehydration solutions have little nutrient value. Molla *et al* (A M Molla, unpublished observations) found that cereal based solutions were superior to the standard glucose based solution in children who were not fed, but their efficacy became similar after introduction of food in the first 24 hours of treatment.

When food based solutions are used proper feeding practices must be emphasised to mothers as they are likely to assume that adequate feeding is being provided to the child during administration of the food based solution. This assumption could be a serious disadvantage of these food based solutions, but we believe that underfeeding is unlikely to occur on a large scale when proper training is given.

While prospective and intensive clinical research is awaited, the next stage of this investigation would be to study the efficacy of a cereal-salt solution with locally available ingredients. The ultimate objective of any programme of oral rehydration is to expand the availability of solutions to every home in developing countries where diarrhoea is a major health problem among children. Mothers should be able to use ingredients available within their kitchens to prepare a solution and to initiate treatment at the very beginning of the onset of a diarrhoeal episode. This will make the programme self sufficient and will minimise the immediate and long term problems seen in children with diarrhoea.

The provision of packets of glucose based solutions to cover every episode of diarrhoea is neither feasible nor affordable at present in Kenya and in Africa at large. Therefore, a simple, effective and traditional home remedy will be the ideal solution for the treatment of diarrhoea.

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# Perinatal mortality in different ethnic groups

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SUMMARY We have analysed the cause of perinatal deaths in four hospitals in the North West Thames region over a six year period commencing January 1980. The Pakistani population had a significantly greater perinatal mortality rate (15·7/1000 births) than the Europeans (11·3/1000 births). This was due to an increased incidence of macerated stillbirths and lethal malformations, the latter resulting from a significantly higher incidence of autosomal recessive disorders, neural tube defects, and renal malformations.

Several studies have shown that there is a higher perinatal mortality rate in the Asian subgroup of the British population.[1-3] This has been attributed to a higher incidence of stillbirths of low birth weight and in deaths due to congenital malformations.[3 4] It has been suggested that greater maternal age, higher parity, lower social class, and a high incidence of consanguineous marriage in the Asian population are aetiological factors in the higher perinatal mortality rate.[1 2] The aims of this study were to assess the contribution of lethal congenital malformations to perinatal mortality in different ethnic groups, to investigate the incidence of definite and probable autosomal recessive syndromes, and to estimate the possible effect of consanguinity.

## Patients and methods

The population studied included all babies born from January 1980 until the end of December 1985 at four hospitals in the North West Thames region. These hospitals were selected because they notified births by ethnic group, which enabled accurate definition of ethnic perinatal mortality rates. The groups studied were Europeans, Pakistanis, and Asians from India. Other groups notified included Asians from Africa and Bangladesh, Chinese, Arabs, Africans, and Vietnamese, but these have not been further subdivided as numbers were too small to permit meaningful analysis.

Perinatal deaths were identified by inspection of the labour ward registers of births (to ascertain all stillbirths) and the neonatal intensive care registers, which recorded all neonatal deaths and transfers to other units. Where babies had been transferred to units not included in the study information regarding their outcome was sought from the receiving hospital. Where possible ascertainment of perinatal deaths was checked against other sources of information such as necropsy files and perinatal mortality meeting records. Maternal and neonatal case records were examined to determine the circumstances of death, necropsy details, karyotype, maternal ethnic group, religion, consanguinity, age, parity, and medical, obstetric, and family history. The genetic case records were examined in cases that had been referred for genetic opinion. Deaths were then classified by cause or mode of death as described by Wigglesworth.[5] This permits classification based on simplified pathological subgroupings to which most perinatal deaths can be provisionally assigned even if necropsy is not done and provides groups with implications for aetiology (table 1). Statistical analysis was performed using Fisher's exact two tailed test and confidence intervals were calculated as described by Morris and Gardner.[6]

## Results

There were 63 442 births in the six year period: 50 164 Europeans (79·0%), 3507 Pakistanis (5·5%), 3367 Indian Asians (5·3%), and 6404 others (10·2%). There was a total of 803 perinatal deaths giving an overall perinatal mortality rate of 12·6/1000 births. The distribution of deaths between the different pathological subgroups is shown in table 1. Four of the babies classified as macerated stillbirths had minor malformations not thought severe enough to cause death. These were mild bilateral hydronephrosis, a small ventricular septal defect, an isolated cleft palate, and a small meningocoele. In 13 (1·6%) cases it was not possible to classify the

Table 1 *Perinatal deaths in different ethnic groups (per 1000 births)*

| *Pathological subgroup* | *European* | *Pakistani* | *Indian* | *Total* (%)* |
|---|---|---|---|---|
| Macerated stillbirths | 142 (2·8) | 17 (4·8)† | 10 (3·0) | 200 (24·9) |
| Congenital malformations | 151 (3·0) | 24 (6·8)† | 11 (3·3) | 209 (26·0) |
| Conditions associated with immaturity | 141 (2·8) | 7 (2·0) | 13 (3·9) | 204 (25·4) |
| Conditions associated with birth asphyxia | 110 (2·2) | 5 (1·4) | 8 (2·4) | 147 (18·3) |
| Other‡ | 21 (0·4) | 2 (0·6) | 1 (0·3) | 30 (3·8) |
| Unclassified | — | — | — | 13 (1·6) |
| Total | 565 | 55 | 43 | 803 |
| Perinatal mortality rate/1000 births | 11·3 | 15·7† | 12·8 | 12·6 |

*Includes perinatal deaths from all ethnic groups.
†Compared with Europeans p<0·05.
‡Rhesus disease, non-immune hydrops, metabolic disorders, etc

deaths because the notes were unobtainable and insufficient information was available from the labour ward and neonatal registers. A total of 543 (67·6%) babies had undergone postmortem examination.

### PERINATAL MORTALITY BY ETHNIC GROUP

The Pakistanis had a significantly higher perinatal mortality rate (15·7/1000 births) than the Europeans (11·3/1000 births) (odds ratio 1·39, 95% confidence interval 1·05 to 1·82, p<0·05). The Indian rate (12·8/1000 births) was not significantly different from that of either of the other groups.

### ETHNIC DIFFERENCES IN PATHOLOGICAL SUBGROUP

There was no significant difference between groups in deaths due to immaturity, birth asphyxial conditions, and other specific causes (table 1). The increased perinatal mortality rate in Pakistanis when compared with Europeans was entirely accounted for by significantly higher incidences of macerated stillbirths (odds ratio 1·67, 95% confidence interval 1·02 to 2·78, p<0·05) and lethal congenital malformations (odds ratio 2·33, 95% confidence interval 1·49 to 3·57, p<0·01). The Indians had slightly higher rates than Europeans in all categories but these did not reach significance.

### ANALYSIS OF LETHAL MALFORMATIONS

During the period of the study 209 babies died as a result of congenital malformations. Postmortem examination had been performed in 150 cases and successful chromosome analysis in 52 cases. Seventy two of these babies were stillborn and 137 died in the neonatal period as a result of their malformations. Table 2 shows the incidence of malformations by system subdivided into ethnic groups. There were significantly higher incidences of neural tube

Table 2 *Malformations divided by system in different ethnic groups and the potential for prenatal detection*[7]

| | *No in study (incidence/1000 births)* | | | *No (%) detectable by prenatal ultrasound* |
|---|---|---|---|---|
| | *European* | *Pakistani* | *Indian* | |
| Central nervous system | 3 (0·06) | 2 (0·57) | 0 | 1 (20) |
| Neural tube defects | 37 (0·73) | 7 (1·99)* | 2 (0·59) | 46 (100) |
| Cardiovascular | 24 (0·48) | 2 (0·57) | 2 (0·59) | 12 (43) |
| Renal | 16 (0·32) | 5 (1·43)** | 2 (0·59) | 12 (52) |
| Pulmonary | 7 (0·14) | 1 (0·29) | 0 | 0 |
| Gastrointestinal | 4 (0·08) | 0 | 1 (0·29) | 4 (80) |
| Musculoskeletal | 12 (0·24) | 0 | 1 (0·29) | 5 (38) |
| Recognised syndromes | 13 (0·26) | 1 (0·29) | 1 (0·29) | 11 (73) |
| Multiple malformations | 16 (0·32) | 4 (1·14)* | 2 (0·59) | 14 (64) |
| Chromosomal | 19 (0·38) | 2 (0·57) | 0 | 5 (24) |
| Total | 151 | 24 | 11 | 110 (59) |

Compared with Europeans *p<0·05, **p<0·01.

defects, renal malformations, and multiple malformations (which were mainly recessive) in the Pakistani population compared with the Europeans, but no significant differences in the incidence of malformations occurring in other systems.

*Central nervous system and neural tube defects*
In 32 of the total of 49 babies in the study with a neural tube defect the diagnosis was made on clinical grounds alone. Three of the babies dying with hydrocephalus had no postmortem examination, destructive procedures having been performed at the time of delivery. In the remaining cases necropsy confirmed the diagnosis. In three cases there had been an affected sibling with a neural tube defect. In one case the mother was an epileptic on phenytoin and phenobarbitone. The incidence of neural tube defects among perinatal deaths in the Pakistani population (2/1000 births) was significantly higher (odds ratio 2·7, 95% confidence interval 1·2 to 6·25, $p<0·05$) than among Europeans (0·74/1000 births) or Indians (0·6/1000 births).

*Cardiovascular*
In 21 of the 29 cardiac cases the diagnosis was confirmed by postmortem examination. In three cases where necropsy was not performed the diagnosis was based on the results of catheterisation or echocardiography. The remaining five babies had been transferred and died at the receiving hospital and insufficient information was available to establish accurately the nature of the cardiac lesion. In two cases there had been a previous affected sibling with congenital heart disease.

*Renal*
Twenty six babies died as a result of renal disorders. The diagnosis was confirmed at necropsy in 20 cases and in the remainder it was made on the basis of the clinical features, antenatal ultrasound findings, or postnatal radiographs and ultrasound. In three cases there was a history of renal malformations in previous siblings. One baby with cystic dysplastic kidneys had a sibling who died in the neonatal period with Potter's syndrome. The histology was reviewed and confirmed cystic dysplasia. One of the babies with prune-belly syndrome was born to a consanguineous couple who already had a child with only one kidney. A consanguineous Pakistani couple had the child with Finnish congenital nephrotic syndrome having had a similarly affected child and another child who was stillborn with cystic dysplastic kidneys. A woman who was an insulin dependent diabetic gave birth to one of the babies with renal agenesis. There was a significantly higher incidence of lethal renal disorders in the Pakistani population compared with the Europeans (odds ratio 4·76, 95% confidence interval 1·72 to 12·5, $p<0·01$).

*Pulmonary*
The diagnosis was confirmed by necropsy in all cases reported here; there was no relevant family history in any of these babies.

*Gastrointestinal*
Postmortem examination had been carried out in all cases. A baby who died with oesophageal atresia was one of twins, the other twin was live born with no abnormalities.

*Musculoskeletal*
In all cases the diagnosis had been confirmed by necropsy and, where relevant, the radiographs and histology had been reviewed by experts. Three of the cases of congenital muscular dystrophy occurred in the same European family. The baby with Pena Shokeir syndrome was born to a consanguineous couple with a previously affected child. A woman known to have myotonica dystrophica had the baby who died with congenital myotonic dystrophy.

*Recognisable syndromes and multiple malformations*
There was no difference in the incidence of recognisable syndromes in the different ethnic groups. There was, however, a significantly higher incidence of multiple malformations with no recognisable syndrome in the Pakistani population when compared with the Europeans (odds ratio 3·57, 95% confidence interval 1·19 to 11·1, $p<0·05$). In three of the four cases which occurred in Pakistanis these were probably recessive syndromes as there had been a previously affected sibling and these cases occurred in consanguineous couples.

*Chromosomal abnormalities*
Abnormal karyotypes were obtained in 16 of the cases described here. A presumptive diagnosis was made in the remaining five cases on the basis of the clinical features (trisomy 13, trisomy 18, two cases of trisomy 21, and triploidy). There was no difference between ethnic groups in the incidence of abnormal karyotypes.

ANALYSIS OF AUTOSOMAL RECESSIVE CONDITIONS (TABLE 3)
There were seven perinatal deaths due to autosomal recessive conditions among the European population (0·14/1000 births). Of these, three babies with congenital muscular dystrophy were born to one couple and there were two siblings that died from megacystis megaduodenum. In the Pakistani

Table 3 *Lethal autosomal recessive conditions*

| | *Consanguinity* | *Race* |
|---|---|---|
| Megacystis megaduodenum[8] | Yes | European (n=2) |
| Pena Shokeir[9] | Yes | European |
| Cystic fibrosis | No | European |
| Congenital muscular dystrophy | No | European (n=3) |
| Congenital muscular dystrophy | No | Indian |
| Neu-Laxova[10] | Yes | Pakistani |
| Finnish congenital nephrosis | Yes | Pakistani |
| I cell disease[11] | Yes | Pakistani |
| Multiple abnormalities | Yes | Pakistani (n=3) |

population there were six deaths due to autosomal recessive syndromes. The three multiple abnormalities with no recognisable syndrome occurred in two different but consanguineous couples. One couple had had a previous affected child (delivered outside the study period) with similar clinical features. The other two lethal multiple malformations were stillborn twins born to a couple who had had a previous stillborn child with similar features. The incidence of deaths due to recessive conditions in Pakistanis (1·71/1000 births) was significantly higher than the European rate of 0·14/1000 births (odds ratio 12·5, 95% confidence interval 4·17 to 33·3, $p<0·0001$). In the Indian population the rate of 0·29/1000 births was not significantly different from the other groups.

### CORRECTED PERINATAL MORTALITY RATES

When corrected for deaths due to autosomal recessive syndromes the Pakistani perinatal mortality rate was 13·7/1000 births as compared with 11·1/1000 in Europeans (odds ratio 1·25, 95% confidence interval 0·94 to 1·67, $p>0·05$). The excess deaths were largely due to malformations and were explained by the higher incidence of neural tube defects in the Pakistani population. The perinatal mortality rates per 1000 births corrected for both neural tube defects and autosomal recessive conditions in the different groups were then 10·4 for Europeans, 11·9 for Pakistanis, and 11·9 for Indians. There was no significant difference between the groups. The higher rate of macerated stillbirths in Pakistanis accounted for the remaining excess in perinatal mortality.

### POTENTIAL FOR PREVENTION

Many of these lethal malformations are amenable to detection in the second trimester either by consideration of the family or medical history followed by appropriate investigations or by routine prenatal ultrasound examination. In 11 cases there was a relevant family history and in six of these referral for expert ultrasound examination should have resulted in prenatal detection. In two cases the mother was an insulin dependent diabetic and in one an epileptic on medication and thus they were at increased risk of having a child with a malformation. There was one baby with trisomy 18 whose mother was 38 years old and this would have been detected had she undergone amniocentesis. Review of the remaining lethal malformations shows that a further 59% could be detected by careful routine prenatal ultrasound performed at 18–20 weeks' gestation (table 2).[7] In the cases reported here only two cases were detected in the second trimester. One was a neural tube defect where the parents elected to continue with the pregnancy and the other was extrophy of the cloaca in one triplet in an in vitro fertilisation pregnancy. It must be remembered, however, that prenatal ultrasound is considerably more sophisticated now in 1989 than it was in the period of the study.

## Discussion

This study has confirmed the higher perinatal mortality rate and shown the significant contribution of lethal malformations in the Pakistani population as reported by others.[2 3] The pattern of malformations found in the three ethnic groups (table 2) confirms an increase in the number of multiple malformations as described by Terry *et al.*[3] We differ, however, in finding of similar rates of chromosomal abnormalities and, in keeping with Gillies *et al*,[2] a significantly higher incidence of neural tube defects in Pakistanis.

Many neural tube defects in this country are now detected by antenatal screening programmes based on routine ultrasound examination in the second trimester or on maternal serum $\alpha$ fetoprotein concentrations. Many women opt for termination of pregnancy when found to have an affected fetus. Lumb *et al* showed that Asian women tended to book later for their antenatal care with 60·7% of them booking after 26 weeks.[1] If this is true of Asian women in other areas it may account for the high contribution of neural tube defects to perinatal mortality as second trimester screening and termination would be available to a relatively smaller proportion of Pakistani women. Furthermore, they may find termination of pregnancy unacceptable on religious grounds.[12] We are currently investigating these hypotheses by examining the ultrasound department records of one of our study hospitals where details of prenatal diagnosis of neural tube defects have been kept and by reviewing the maternal case notes of women who had affected babies.

We have shown the significant contribution of autosomal recessive syndromes to perinatal mortality in the Pakistani population. It is of note that all the autosomal recessive disorders occurring in this group were in babies born to consanguineous couples, as indeed were half of those in the European population. In Bradford, Gillies *et al* showed that 48% of Pakistani marriages were between first cousins compared with 8% of Indian marriages and 0·5% of non-Asians.[2] A similar pattern has been reported in Birmingham.[3] In our study we have incomplete ascertainment of consanguinity rates because only one of the four hospitals routinely made direct enquiry of consanguinity. The others only recorded it as a positive finding. Accurate information was also available from those couples who had received genetic counselling. Our findings with regard to consanguinity are shown in table 4, which confirms the trend found in Bradford and Birmingham. These observations indicate that consanguinity has an important influence on the excess perinatal mortality in Pakistanis, but a prospective study with complete ascertainment of consanguinity rates in all ethnic groups is required before this can be proved.

After correction of perinatal mortality rates for autosomal recessive syndromes and neural tube defects there still remains an excess of perinatal deaths in the Pakistani population compared with Europeans. This is largely due to a significantly higher incidence of normally formed macerated stillbirths. As more European (72%) than Pakistani (50%) perinatal deaths underwent postmortem examination, relatively more internal malformations may have been missed in the latter group. Furthermore the Pakistani population may have been subject to influences such as higher parity, shorter pregnancy interval, and greater maternal age as described by Lumb *et al*,[1] and to which a higher perinatal mortality may be attributed.[13]

While this study confirmed the higher perinatal mortality rate in the Pakistani population it failed to show a similar significant trend in Indian Asians as reported by Terry *et al.*[14] Explanations for these different observations include differences in both social class and religion between the two Indian populations studied. Most Indians in Birmingham are Punjabi Sikhs in social class 4 and 5,[15] whereas in the study reported here they are mainly Hindu and fall into social class 2 and 3 (J Chapple, personal communication). The appreciable differences in cultural and social classification may partly explain the observed discrepancies between the two studies as there is an association between low social class and higher perinatal mortality rates,[13] and dietary differences may affect maternal nutritional status.[16]

Table 4 *Consanguinity rates (%)*

| | *Consanguineous* | *Non-consanguineous* | *Unknown* |
|---|---|---|---|
| European | 1·2 | 16·9 | 81·9 |
| Pakistani | 25·9 | 3·7 | 70·4 |
| Indian | 0 | 23·3 | 76·7 |

What practical steps may taken to reduce the excess risk in the Pakistani population? It seems unlikely that structure of society and the incidence of consanguinity will change in the immediate future—indeed a recent study has suggested that there is an increasing rate of consanguineous marriage in Pakistanis in West Yorkshire.[17] We should therefore direct our attention towards measures such as vitamin supplementation for Asian women both before and during pregnancy as this may help reduce the contribution from neural tube defects.[18] Preconceptional and genetic counselling, and expert second trimester ultrasound, should be readily available for all Pakistani women. Their risk of having a baby die in the perinatal period as a result of a congenital malformation is one in 150, which is higher than the risk level at which screening for Down's syndrome is currently offered on the grounds of maternal age. Those women who have a consanguineous marriage appear to be at greater risk. In this study of the 14 perinatal deaths that occurred in consanguineous Pakistani families 10 were due to congenital malformations.

Finally we would urge that full assessment including photography, radiology, cytogenetics, and detailed necropsy of babies who die in the perinatal period should be undertaken to enable accurate diagnosis. This would ensure that parents are fully informed of the risks for future pregnancies and enable the relevant prophylactic and diagnostic facilities to be made available to them.

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# Growth and development in premature twins

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SUMMARY A total of 476 infants (386 singletons and 90 twins) born before 32 weeks' gestation were studied to compare long term growth and development in twins and singletons. At 18 months, after adjusting for confounding social, obstetric, and neonatal factors, twins were not disadvantaged in their neurodevelopmental status, but were 1·6 cm shorter than singletons and had thicker triceps and subscapular skinfolds. No significant differences were found between first and second born twins in later growth or development at 18 months post-term. While preterm twins may have an inherent disadvantage in linear growth it is suggested that in other respects twinning is not a risk factor in preterm infants.

There is considerable evidence that twins are disadvantaged in terms of perinatal mortality,[1] long term growth,[2-4] and neurodevelopmental status.[3 4] This may reflect the increased risk of antenatal complications, preterm delivery, and low birth weight in twin pregnancies.[5] Fifty per cent of all twins are of low birth weight, compared with 6% of singletons,[2] and twins account for about 20% of infants under 32 weeks' gestation (see below). In view of this high frequency of twins within the population of premature babies, and the lack of available data, we considered it important to identify whether twinning was a 'risk factor' for an adverse outcome in infants born preterm. In a study on a cohort of surviving infants born before 32 weeks' gestation we have examined obstetric and neonatal course together with development and growth performance at 18 months post-term. By adjusting for the social, obstetric, and neonatal differences between preterm twins and singletons, we have investigated whether outcome at 18 months differs between the two groups. Furthermore, we considered that our data might throw light on the more general question of whether there is an inherent disadvantage in being a twin or whether the poorer prognosis reported in twins might be related principally to the increased incidence of preterm delivery.

## Subjects and methods

Infants born before 32 weeks' gestation from five centres (Cambridge, Ipswich, Kings Lynn, Norwich, and Sheffield) were entered into this study if they survived until discharge from the neonatal unit and were from singleton or twin pregnancies (higher order multiple births were excluded). They came from a larger cohort enrolled in a trial of preterm infant feeding between 1982 and 1984,[6] for whom extensive data had been collected on antenatal factors, delivery, and postnatal events.

Social class of the family was coded using the Registrar General's classification,[7] social class 3 being subdivided into manual and non-manual. Mother's education was classified in 5 grades: 1=no educational qualifications, 2=up to four passes for the Certificate of Secondary Education (CSE), 3=any O levels or more than four passes for CSE, 4=any A levels, and 5=degree or higher professional qualification. The child's birth rank in the living children of the family was recorded, with twins being assigned equal rank.

Surviving infants were invited to a follow up appointment at 18 months from expected date of delivery. Infants from the East Anglian centres were seen by RM; RP supervised follow up in Sheffield. A medical and developmental history and extensive physical examination were undertaken. Naked weight, supine length, occipitofrontal head circumference, and triceps and subscapular skinfold thickness were measured. Bayley mental and motor scales were administered,[8] together with the academic scale of Developmental Profile II.[9] Scores were calculated using the infants' ages from expected date of delivery. The Bayley mental scale, like most infant tests, requires age-appropriate fine motor skills. It is therefore of limited use in infants with cerebral palsy. The academic scale of Developmental Profile II, a questionnaire based test, depends much less on fine motor skills at this age. Mean Bayley mental scores were therefore calculated for neurologically normal infants, whereas mean Intelligence Quotient (IQ) equivalent (from Developmental Profile II) was calculated for all infants.

Student's *t* test and the $\chi^2$ test were used for univariate statistical analyses except in the case of Apgar score, when the Wilcoxon rank sum test was used. Multiple regression analyses were used to evaluate outcome; linear regression for continuous dependent variables and logistic regression for dichotomous dependent variables.

## Results

Altogether 476 infants, 386 singletons and 90 twins (19%), were enrolled in this study. Eight infants (six singletons and two twins) died after leaving the neonatal unit and before the 18 month assessment. The two groups of survivors (88 twins compared with 380 singletons) had similar mean (SD) birth weight (1281 (265) g compared with 1277 (291) g) and gestational age (29·2 (1·7) weeks compared with 29·2 (1·5) weeks). Males accounted for 59% of twins and 49% of singletons. Seventy two of the twins were from 36 surviving pairs, 16 were from pairs where the other twin had died (four stillborn, 11 neonatal deaths, and one later death).

Table 1 shows those social, obstetric, and neonatal factors that were significantly associated with twins.

Table 1 *Social, obstetric, and neonatal factors associated with twins. Results are No (%) except where otherwise stated*

| | *Twins (n=88)* | *Singletons (n=380)* | *p Value* |
|---|---|---|---|
| Social factors: | | | |
| No previous living children | 69(78) | 191(50) | <0·001* |
| Obstetric factors: | | | |
| Primiparous mother | 51(58) | 131(34) | <0·01* |
| Pregnancy induced hypertension | 4(5) | 71(19) | <0·05* |
| Antepartum haemorrhage | 8(9) | 102(23) | <0·05* |
| Steroids (maternal) | 25(28) | 53(14) | <0·05* |
| Spontaneous onset of labour | 74(84) | 236(62) | <0·01* |
| Caesarean delivery | 29(33) | 181(48) | <0·05* |
| Neonatal factors: | | | |
| Mean (SD) temperature on admission to special care baby unit (°C) | 36(0·7) | 35·7(0·9) | <0·005† |
| >5 Days in over 30% oxygen | 34(39) | 192(51) | <0·05* |

*By $\chi^2$ test; † by *t* test.

Statistical analysis of maternal factors included mothers of twins once. Other social and obstetric factors found not to be associated with twinning were: mother's age, educational level or marital status, social class, bleeding in the first trimester of pregnancy, and prolonged rupture of membranes or breech delivery. In the neonatal period no significant differences were found between twins and singletons in Apgar score at 5 minutes, the proportion who were small for gestational age, or required mechanical ventilation for more than five days.

Follow up data were collected on 354/380 (93%) singletons and 82/88 (93%) twins. Table 2 shows the outcome differences between twins and singletons. There were no significant differences in neurodevelopmental status or weight whereas head circumference and triceps and subscapular skinfold thickness were significantly greater in twins and length was significantly less in twins. While the outcome data in table 2 are shown for descriptive purposes, the comparison between twins and singletons is highly confounded. (For instance, the difference in sex ratio (above) would increase the observed difference in length and decrease that for head circumference.)

Regression models were used, therefore, to determine whether there were significant differences between twins and singletons in terms of growth or development at 18 months post-term, after adjusting for possible confounding factors, including sex of infant and all those listed above and in table 1. Stepwise regression was used so that only those factors significantly related to each outcome were included in the final model. After adjusting for these factors, being a twin was not significantly associated

Table 2 *Outcome in twins and singletons at 18 months post-term. Results are mean (SE)*

| *Outcome measure* | *Twins (n=82)* | *Singletons (n=354)* | *p Value* |
|---|---|---|---|
| Cerebral palsy | 10/82 | 35/354 | 0·48 |
| Bayley mental developmental index* | 100·8 (2·2) | 101·2 (1·1) | 0·88 |
| Bayley psychomotor developmental index* | 91·6 (2·0) | 93·4 (0·9) | 0·43 |
| IQ equivalent | 105·0 (1·9) | 105·2 (0·9) | 0·89 |
| Weight (kg) | 10·1 (0·2) | 10·2 (0·07) | 0·75 |
| Length (cm) | 79·0 (0·4) | 79·9 (0·2) | <0·05 |
| Head circumference (cm) | 48·4 (0·2) | 48·0 (0·09) | <0·05 |
| Triceps skinfold thickness (mm) | 8·4 (0·2) | 7·9 (0·1) | <0·05 |
| Subscapular skinfold thickness (mm) | 5·8 (0·1) | 5·4 (0·06) | <0·05 |

*Children with cerebral palsy were excluded from these comparisons by *t* test.

Table 3 *Significant effects of being a twin on anthropometry at 18 months post-term: regression analysis*

| *Measurement* | *Effect of being a twin (95% confidence interval)* | *p Value of regression coefficient* |
|---|---|---|
| Length (cm) | −1·59 (−0·77 to −2·41) | <0·005 |
| Mean skinfold thickness (mm) | +0·52 (0·07 to 0·97) | <0·03 |

*Mean skinfold thickness is the mean of triceps and subscapular measurements.

with weight or head circumference at 18 months. There was a marginally significant association with triceps skinfold thickness ($p<0{\cdot}06$) and significant associations with length ($p<0{\cdot}005$), subscapular skinfold thickness ($p<0{\cdot}05$), and mean of triceps and subscapular skinfold thickness ($p<0{\cdot}03$) (table 3), twins being shorter and fatter than singletons.

Being a twin, rather than singleton, was not significantly associated with the incidence of cerebral palsy, Bayley mental or psychomotor developmental indices (in the neurologically normal infants), or IQ equivalent.

There were 45 first twins and 43 second twins, of whom 41 in each group were seen at 18 months post-term. Second twins were significantly more likely than first to be breech deliveries (1/45 compared with 8/43, $p<0{\cdot}05$). Apgar score at 5 minutes was significantly lower for second twins ($p<0{\cdot}02$). At 18 months post-term there were no significant anthropometric differences between first and second twins. Mean (SD) weight for second twins was 9·9 (1·5) kg compared with 10·3 (1·4) kg for first, mean length was 78·4 (3·4) cm compared with 79·4 (3·1) cm, and mean head circumference was 48·2 (1·4) cm compared with 48·5 (1·5) cm. There were no significant differences in neurodevelopmental outcome; cerebral palsy was diagnosed in 4/41 first and 6/41 second twins. Mean Bayley mental developmental index was 100·5 (16·7) in first twins and 101·1 (19·3) in second.

## Discussion

It is commonly thought that preterm twins have a worse prognosis than preterm singletons. Our study shows, however, that for most factors analysed, this is not the case. Nevertheless, within the population of infants born before 32 weeks' gestation significant differences have emerged between premature twins and singletons. There were significant social, obstetric, and neonatal differences between twins and singletons, shown in table 1. These differences are broadly similar to those shown in previous studies,[10 11] though the lower incidence of pregnancy induced toxaemia and greater proportion of primiparae in mothers of preterm twins contrasts with data relating to twin pregnancies of all gestations.[12]

After adjusting for confounding factors, twins were shorter and had thicker subscapular skinfolds than singletons at 18 months' post-term. Silva *et al* found that twins were shorter, lighter, and had smaller head circumferences than singletons at 3, 5, 7, 9, and 11 years,[3 4] although these results could have been explained by the lower mean birth weight and shorter mean gestation in the twin group. We have shown the differences in length and skinfold thickness are still present when preterm twins are compared with preterm singletons and after adjustment for other factors.

The principal observation in this study, however, was that there was no significant differences between preterm twins and singletons in neurodevelopmental outcome, either before or after adjusting for confounding factors. Thus there was no difference in the incidence of cerebral palsy, in Bayley mental or psychomotor indices, or in IQ equivalent. These data contrast with those reported for twins of all gestations inclusive,[3 4] in whom there was a significant neurodevelopmental disadvantage, but support those of Alberman who found that in children born before 32 weeks' gestation the risk of cerebral palsy was not significantly greater among twins than singletons.[13]

In a comparison of first and second twins it was found that second twins were more likely to be delivered by the breech and had significantly lower Apgar scores at 5 minutes. This did not, however, lead to any significant neurodevelopmental disadvantage at 18 months' post-term. Second twins were generally smaller at this age, but none of the anthropometric differences reached significance.

A gestational age cut off was used for this report because, if we had used the 1850 g birth weight cut off on which the whole study cohort was based,[6] only the smaller twin from some pairs would have been included. We were interested to find, however, that when the same analyses were done using the whole cohort under 1850 g birth weight (596 singletons compared with 156 twins) there were no significant differences in neurodevelopmental outcome, but the twins were again significantly shorter at 18 months' post-term, and had significantly thicker triceps and subscapular skinfolds. We suggest that twins have an intrinsic disadvantage in subsequent linear growth and that the length differences seen in other studies are not entirely due to the lower mean gestation and birth weight of twins. In contrast we did not find evidence of a neurodevelopmental disadvantage for preterm twins compared with preterm singletons. We suggest that the developmental disadvantage seen for twins in other studies may be due to the increased prevalence of preterm delivery in these infants, and may not reflect an inherent disadvantage for babies from twin pregnancies.

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# Left ventricular function in β thalassaemia major

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SUMMARY The left ventricular dimension and posterior wall dynamics were studied by computer assisted analysis of M mode echocardiography in 25 normal children (group 1) and 32 transfusion dependent children with β thalassaemia major who had no evidence of heart failure (group 2). Twenty seven of those in group 2 remained well but five died of cardiac decompensation within 12 months. Compared with group 1, the left ventricular fractional shortening and ejection fraction were normal in those in group 2 who survived but diminished in those who died. Evaluation of left ventricular dimension and posterior wall dynamics during systole (peak shortening rate, peak velocity of circumferential fibre shortening, and peak posterior wall thickening rate) showed similar findings in that only the group who died had abnormal values. The left ventricular dimension and posterior wall diastolic dynamics (peak relaxation rate, normalised peak relaxation, peak wall thinning, and normalised peak wall thinning rate), however, showed progressively slower rates in all the children in group 2. The findings suggest that left ventricular diastolic dysfunction occurs early in myocardial impairment in patients with β thalassaemia major. When there are abnormalities in both diastole and systole, the myocardial impairment is advanced and the prognosis is poor.

Iron overloading is inevitable in children with β thalassaemia major because of repeated blood transfusions and enhanced gastrointestinal absorption. When cardiac impairment from iron deposition is severe enough to be clinically obvious, the disease is advanced and the subsequent survival is brief.[1 2] Henry *et al* used conventional M mode echocardiography to study these patients and found that most had normal resting left ventricular ejection fractions; some who had low values, however, died within six months.[3] Leon *et al* used radionuclide cineangiography to measure the left ventricular ejection fraction during exercise and found that the index in the thalassaemic patients did not increase as in normal subjects but either dropped or remained unchanged.[4] Normally, however, the ejection fraction does not change appreciably during submaximal exercise, and it is often difficult to exercise young children enough. Computer assisted analysis of M mode echocardiography, developed by Gibson and Brown,[5] has been used to evaluate left ventricular function in various kinds of myocardial diseases,[6–14] but its use in children with β thalassaemia major has not been reported. We report our experience with computer assisted analysis of M mode echocardiography to evaluate the left ventricular function in these patients.

## Patients and methods

The subjects were divided into two groups. Group 1 comprised 25 normal schoolchildren to serve as controls. Group 2 comprised 32 children with homozygous β thalassaemia who needed regular blood transfusion; none had clinical evidence of heart failure and at the time of study none was on iron chelation treatment. In the follow up period, 27 in group 2 remained well but five developed overt congestive heart failure and died within 12 months of the initial echocardiographic study. The two groups were comparable for age, sex, weight, and height (table 1).

The echocardiographic study was performed by one of us (KCL) when the subjects were at rest, and in group 2 one week after a blood transfusion when their haemoglobin concentration was more than 110 g/l. If the Hg concentration was less than this, the echocardiographic study was not carried out. Electrocardiogram, phonocardiogram, and cross-sectional echocardiograms were carried out with an Advanced Technology Laboratory MK 600 sector scanning system. Firstly, a subjective assessment of left ventricular regional contraction was obtained by using the left ventricular long axis, short axis and apical four chambered views. To obtain the M mode

Table 1 *Comparability of the groups*

| | *Group 1* | *Group 2* | |
|---|---|---|---|
| | | *Survived (n=27)* | *Died (n=5)* |
| Mean (range) age (years) | 9·5 (7–13) | 10·5 (6–14) | 12·8 (11–16) |
| Sex: | | | |
| Male | 13 | 15 | 2 |
| Female | 12 | 12 | 3 |
| Weight (kg) | 19·5–35 | 18·4–34·5 | 22–34 |
| Height (cm) | 115–140 | 108–134 | 120–139 |

echocardiographic tracings, the M mode ultrasonic beam was directed along the centre of the left ventricular short axis at the level of the tip of the mitral valve. The M mode echocardiographic tracings were recorded with maximal expansion together with the phonocardiograms and electrocardiograms at a paper speed of 100 mm/s. Only those high quality tracings with uninterrupted endocardial and epicardial surfaces were chosen. The echocardiograms were digitised by the method of Gibson and Brown[5] with a Hewlett Packard 9874A digitiser (resolution 0·0025 cm, relative accuracy 0·0125 cm) and processed by a Hewlett Packard 9836A computer. End diastole and end systole were taken to occur at the onset of Q wave of the electrocardiogram and A2 of the phonocardiogram, respectively. The left ventricular posterior septal endocardial and posterior wall endocardial and epicardial surfaces were digitised continuously. The digitised data were plotted with a Hewlett Packard 2671G graphic printer (figure). If the plot was satisfactory and free from artefacts, the left ventricular dimension, posterior wall thickness, and their respective rates of change with time were determined; otherwise, the digitisation was repeated. At least three consecutive cardiac cycles were digitised and the mean value calculated. The following indices of left ventricular dimension and posterior wall were obtained:

(A) Conventional left ventricular M mode echocardiographic indices—(1) end diastolic dimension, (2) end systolic dimension, (3) fractional shortening (1−end systolic dimension/end diastolic dimension), (4) ejection fraction (calculated from the formula of Teichholtz *et al*[15]), (5) end diastolic wall thickness, (6) end systolic wall thickness, and (7) wall fractional thickening (end systolic wall thickness/end diastolic wall thickness)−1.

(B) Left ventricular dimension dynamic indices—(1) Systole (a) peak dimension shortening rate (peak systolic rate of left ventricular dimension change), and (b) peak velocity of circumferential fibre shortening (peak systolic rate of left ventricular dimension change/end diastolic dimension). (2) Diastole (a) peak dimension relaxation rate (peak diastolic rate of left ventricular dimension change), and (b) normalised peak dimension relaxation rate (peak diastolic rate of left ventricular dimension change/end diastolic dimension).

(C) Left ventricular posterior wall dynamic indices—(1) Systole (a) peak wall thickening rate (peak systolic wall thinning rate), and (b) normalised peak wall thickening rate (peak systolic wall thickening rate/end diastolic wall thickness). (2) Diastole (a) peak wall thinning rate (peak diastolic wall thinning rate), and (b) normalised peak wall thinning rate (peak diastolic wall thinning rate/end diastolic wall thickness).

In 10 patients the echocardiographic examination and digitisation were repeated by the same worker (KCL) and the results of the two studies were compared.

The results for both groups were expressed as the mean (1 SD), and the *t* test (Bonferroni[16]) was used for comparison. The differences were taken to be significant when the p value was $<0{\cdot}05$.

## Results

The mean heart rates in the two groups were similar.

### CONVENTIONAL M MODE ECHOCARDIOGRAPHIC INDICES (TABLE 2)

The mean end diastolic dimension and end systolic dimension of those in group 2 who survived were significantly larger than those in group 1 ($p<0{\cdot}05$). Likewise the corresponding values among those in group 2 who died were also significantly larger than in both group 1 and group 2 who survived. The fractional shortening and ejection fraction of group 2 who survived were not significantly different from those in group 1, but those of group 2 who died were significantly diminished ($p<0{\cdot}001$).

Although the mean end diastolic wall thickness of group 2 (particularly those who died) was significantly greater than group 1, the mean end systolic wall thickness of the three groups was not significantly different. Thus the left ventricular wall fractional thickening was significantly reduced in group 2 survivors ($p<0{\cdot}01$) and even more reduced in group 2 patients who died ($p<0{\cdot}001$).

### LEFT VENTRICULAR DIMENSION DYNAMIC CHANGES (TABLE 3)

The systolic dynamic changes (peak dimension shortening rate and velocity of circumferential fibre shortening) of group 2 survivors were not significantly different from group 1, but only group 2

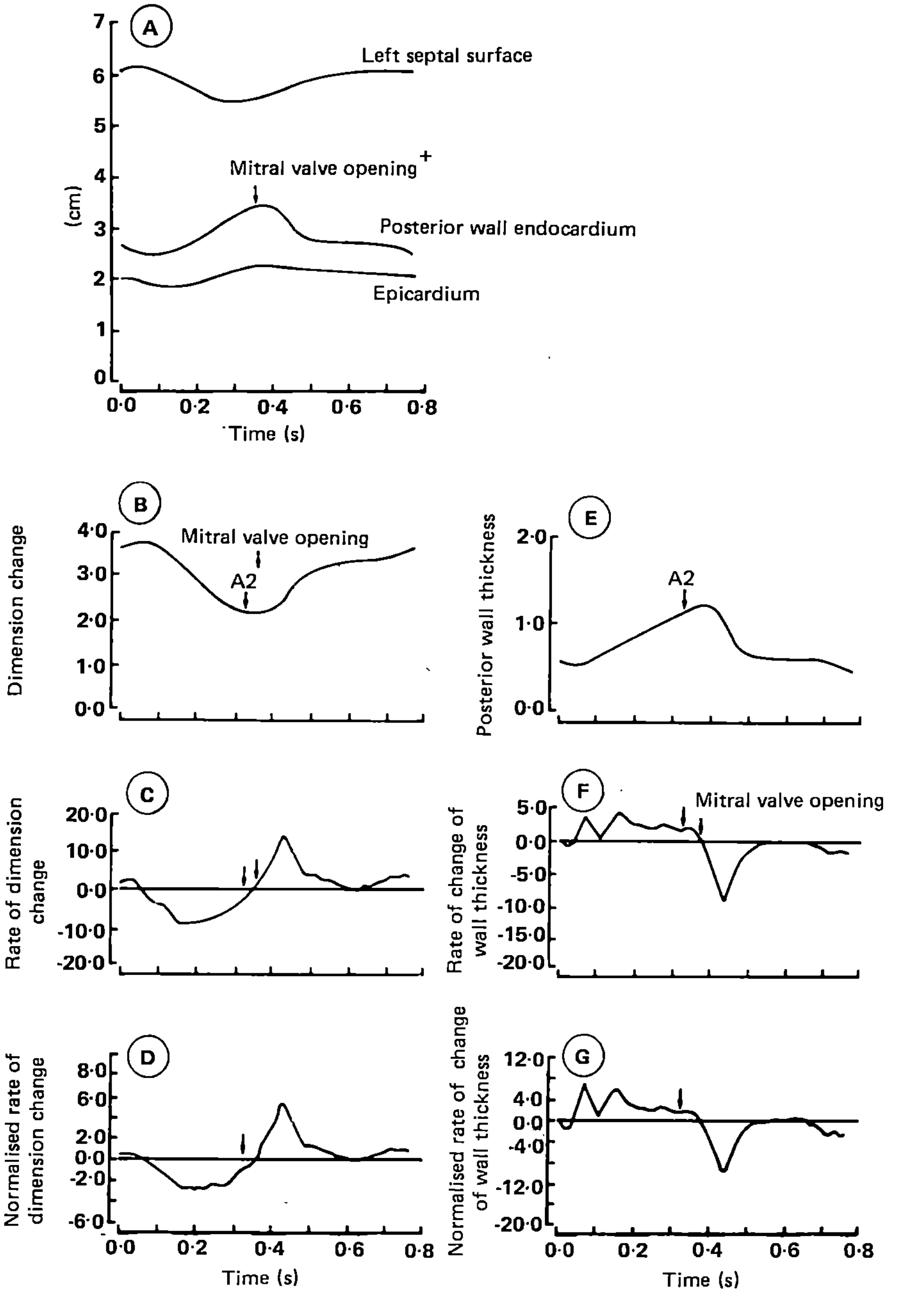

Figure *After digitisation the computer plots out the echogram (A). If the plot is satisfactory it will then plot the dimension change (B); the rate of dimension change (C); the normalised rate of dimension change (D); the posterior wall thickness (E); the rate of change of wall thickness (F); and the normalised rate of change of wall thickness (G).*

patients who died showed significantly abnormal values (p<0·05 and p≥0·01, respectively). The diastolic dynamic changes, however (peak dimension relaxation rate and normalised peak dimension relaxation rate) of group 2 survivors were already depressed (p<0·01 and p<0·001, respectively) and those of group 2 who died were more depressed.

### LEFT VENTRICULAR POSTERIOR WALL DYNAMIC CHANGES (TABLE 4)

The systolic peak wall thickening rate and the normalised value among the various groups were not significantly different. The diastolic peak wall thinning rate of group 2 survivors, however, was already significantly slower than group 1 (p<0·001), while that of group 2 patients who died was more

Table 2 *Conventional indices of M mode echocardiography*

| *Mean (SD) measurement* | *Group 1* | *Group 2* | | *p Values* | | |
|---|---|---|---|---|---|---|
| | | *Survived* | *Died* | *Group 1 v group 2, survived* | *Group 1 v group 2, died* | *Group 2, survived v group 2, died* |
| Left ventricular end diastolic dimension (cm) | 3·87 (0·33) | 4·25 (0·57) | 5·07 (0·57) | <0·05 | <0·001 | <0·001 |
| Left ventricular end systolic dimension (cm) | 2·45 (0·17) | 2·82 (0·5) | 3·92 (0·6) | <0·05 | <0·001 | <0·001 |
| Fractional shortening (%) | 35·5 (4·5) | 33·0 (3·8) | 22·25 (7·5) | <0·05 | <0·001 | <0·001 |
| Ejection fraction | 64·0 (5·0) | 59·5 (7·5) | 37·05 (17·0) | >0·1 | <0·001 | <0·001 |
| Left ventricular wall end diastolic thickness (cm) | 0·41 (0·06) | 0·52 (0·1) | 0·7 (0·27) | <0·01 | <0·001 | <0·01 |
| Left ventricular wall end systolic thickness (cm) | 0·95 (0·1) | 1·02 (0·17) | 1·05 (0·27) | >0·3 | >0·5 | >0·9 |
| Wall fractional thickening | 1·35 (0·25) | 1·0 (0·39) | 0·54 (0·26) | <0·01 | <0·001 | <0·05 |

Table 3 *Left ventricular dimension dynamics*

| *Mean (SD) measurement* | *Group 1* | *Group 2* | | *p Values* | | |
|---|---|---|---|---|---|---|
| | | *Survived* | *Died* | *Group 1 v group 2, survived* | *Group 1 v group 2, died* | *Group 2, survived v group 2, died* |
| Peak left ventricular shortening rate (cm/s) | 8·79 (1·50) | 8·84 (1·88) | 6·69 (1·78) | >0·9 | <0·05 | <0·05 |
| Peak velocity of circumferential fibre shortening (circumference/s) | 2·2 (0·5) | 2·1 (0·4) | 1·3 (0·3) | >0·9 | <0·001 | <0·01 |
| Peak left ventricular dimension relaxation rate (cm) | 16·34 (4·10) | 12·80 (2·90) | 8·9 (2·3) | <0·01 | <0·001 | <0·02 |
| Normalised peak left ventricular dimension relaxation rate (circumference/s) | 4·2 (1·0) | 3·1 (0·6) | 1·9 (0·8) | <0·001 | <0·001 | <0·02 |

Table 4 *Left ventricular posterior wall dynamics*

| *Mean (SD) measurement* | *Group 1* | *Group 2* | | *p Values* | | |
|---|---|---|---|---|---|---|
| | | *Survived* | *Died* | *Group 1 v group 2, survived* | *Group 1 v group 2, died* | *Group 2, survived v group 2, died* |
| Peak wall thickening rate (cm/s) | 3·69 (0·75) | 3·62 (0·81) | 3·75 (1·2) | >0·9 | >0·9 | >0·9 |
| Normalised peak wall thickening rate/s | 6·4 (1·3) | 5·38 (1·5) | 4·64 (2·6) | >0·05 | >0·05 | >0·05 |
| Peak wall thinning rate (cm/s) | 11·56 (2·8) | 6·92 (2·3) | 4·64 (0·8) | <0·001 | <0·001 | <0·05 |
| Normalised peak wall thinning rate/s | 29·1 (8·2) | 14·0 (5·8) | 7·2 (1·7) | <0·001 | <0·001 | <0·05 |

depressed ($p<0.05$). The same was true when the peak wall thinning rate was normalised by the left ventricular wall end diastolic thickness.

Cross sectional echocardiographic evaluation of left ventricular motion showed no dyskinesia in any of the subjects studied.

The mean intraobserver variation of all the static indices between two studies of the same patient was 4·5 (1·5)% and that of dynamic indices was 7·5 (2)%.

## Discussion

Desferrioxamine given subcutaneously was first introduced to treat thalassaemic patients in our unit in 1979, and by now almost all patients are on iron chelation treatment at home. Since 1981 these patients have had regular echocardiographic studies, and the data in the present report represent our earlier experience with patients before chelation treatment was started. The patients were grouped retrospectively according to their outcome because it seemed reasonable to assume that the myocardial state of group 2 patients who subsequently died of cardiac compensation was preterminal, while that of the group 2 survivors was only mildly deranged. Thus theoretically the patients studied had different degrees of myocardial dysfunction. Although the mean age of the group 2 patients who died was marginally greater than the other groups, their mean body sizes (height and weight) were not significantly different.

Computer assisted analysis of M mode echocardiography is an established method of assessing myocardial function. It has been used to study a large variety of cardiac disorders in both adults and children.[6–14] Provided that adequate precautions are taken (selecting only the good quality echocardiographs with continuous leading edges of the septal and wall surfaces for digitisation, high speed recording of maximally expanded echocardiographic tracings, recording the left ventricular endocardium at the level of the tip of the mitral valve as a constant site of reference, and taking the mean of the results of at least three cardiac cycles) the results obtained are reliable, reproducible, and interpretable. The reproducibility of computer assisted analysis of M mode echocardiography has been previously shown[17] and the present study confirms it. As only one of us (KCL) was responsible for recording and digitising the echocardiographs, the variation was low. The rates of systolic and diastolic changes vary little with heart rate[14]; these indices, which are obtained by non-invasive means, may be ideal for monitoring myocardial performance. The method, however, has not previously been used to evaluate the myocardial function of thalassaemic patients.

Dilatation of left ventricular chambers in patients with thalassaemia has previously been shown,[1–3] and the results of the present study confirm this. Henry *et al* showed that the fractional shortening or ejectional fraction, which were better indices of myocardial function, were only abnormal when the myocardial impairment in thalassaemia was extreme.[3] This phenomenon was also confirmed by our results, as those indices were still normal in group 2 survivors, but abnormal in those who died. We also found that although both the systolic and diastolic dimensional and posterior wall dynamic indices were abnormal in those with preterminal myocardial dysfunction, abnormalities of the diastolic dynamic indices alone were already present. The diastolic abnormalities seemed to become more pronounced as the myocardial impairment worsened. When the diastolic indices were normalised by the corresponding end diastolic dimension or wall thickness, an attempt to take account of chronic volume overloading and body sizes made the abnormalities more obvious. There was, however, considerable overlap among groups. Further evaluation in a longitudinal manner is necessary to confirm the usefulness of the method in monitoring these patients' myocardial function.

The phenomenon of abnormal left ventricular diastolic function with otherwise normal systolic function detected by computer assisted analysis of M mode echocardiography has been shown in such conditions as systemic hypertension and postoperative aortic stenosis, in which pathological left ventricular hypertrophy is present.[6 7] Using the same method, Shapiro and Smith have shown that in normal subjects physiological hypertrophy of the left ventricular wall from physical training does not give rise to any early diastolic abnormalities.[17] These studies confirm our belief that the depressed diastolic indices found in our group 2 patients who survived are evidence of myocardial impairment from iron deposition rather than the simple result of myocardial hypertrophy secondary to chronic anaemia. Our evaluation of a small group of patients with thalassaemia intermedia who were chronically anaemic but who were not receiving blood transfusions showed normal diastolic findings, which accords with this suggestion (unpublished observations). Additionally, our present finding of a progressive increase in end diastolic wall thickness in group 2 without the corresponding increase in end systolic wall thickness has similar implications. This again suggests that the isolated increase in end diastolic wall thickness is not the result of simple hypertrophy of the myocardial contractile fibres alone, otherwise both their end systolic and end diastolic wall thicknesses would be correspondingly increased. Their myocardiums must have contained an appreciable proportion of non-contractile tissue, possibly reactive or replacement fibrosis, or both, together with myocardial cell death secondary to myocardial iron deposition. This is in keeping with the pathological findings in hearts with haemochromatosis.[18] Thus it is likely that the diastolic abnormalities found in the thalassaemic patients are the early functional result of such a pathological process. When both the diastolic and systolic functions are affected, severe myocardial cell loss and fibrosis must have been present. Whether fibrosis will regress with successful iron removal by chelation is unknown. If the answer is no, iron chelation treatment may only halt the progression of myocardial dysfunction that is already present rather than reverting it. This would imply that optimal treatment of thalassaemic patients should include early institution of iron chelating drugs well before the development of any myocardial dysfunction. Further longitudinal studies are required to clarify the issue.

Grossman and Mclaurin suggested that many of the signs and symptoms of cardiac failure that had previously been attributed to abnormal early systolic performance may be caused largely by altered diastolic properties of the ventricular chambers.[19] Our findings confirm this, and point to the importance of evaluating the diastolic functions of the transfusion dependent thalassaemic patients. Our results show that with the use of computer assisted analysis of M mode echocardiography, abnormalities of left ventricular function are detected in children with β thalassaemia major before their myocardial dysfunction becomes overt. Abnormalities in diastole appear earlier and may be used to differentiate different grades of myocardial dysfunction. When both the diastolic and systolic abnormalities are present the myocardial dysfunction is terminal and the prognosis is poor. Our study should stimulate further research to validate the usefulness of the method used and to cast further light on the mechanisms of myocardial dysfunction as well as the effect of iron chelation treatment in these patients.

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# Incidence of contraindications to immunisation

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SUMMARY A cohort of 522 children entering primary school were reviewed for contraindications to immunisation. Every child in the group would have been eligible to receive diphtheria, tetanus, polio, and measles immunisation if the current (1988) Department of Health and Social Security (DHSS) guidelines had been followed. Only 2·5% of the cohort met the DHSS contraindications to pertussis immunisation.

An effective immunisation programme must be a major aim of any public health organisation. For those vaccines which are currently used in this country there are recognised contraindications which are published by the DHSS.[1] Previously published contraindications have often been misinterpreted.[2 3]

All the vaccines protect the individual but pertussis, polio, and measles immunisation offer further protection by reducing the circulation of the infecting organism in the community. In an attempt to increase this 'herd immunity' the European Regional Committee of the World Health Organisation has recommended a target of a 90% uptake of primary immunisations for all children under 2 years by the year 1990.[4]

There remains, however, a paucity of data as to the possibility of achieving these goals in the face of published guidelines. This study looked at a cohort of children to find the prevalence of DHSS contraindications to immunisation within the normal school population.

## Subjects and methods

All children entering state education with Hampshire Education Authority are offered a preschool entrance medical. This follows a similar format to those outlined elsewhere[5] and takes place between the ages of 4 and 6 years.

Those children entering normal primary school in two areas of the education authority were included in the study. All were born between August 1980 and July 1981 and started school over a three term period. Children who attended schools for special education outside the area were not included.

The interview with the parents sought contraindications to immunisation and these histories were then compared against the newly published DHSS contraindications to immuisation.[1] With respect to pertussis it was assumed that those children with 'problem histories' would have been advised against immunisation. The immunisation status of the child was checked against centrally held computer data.

For those children who failed to receive their immunisations the reasons given were divided into recognised DHSS contraindications, inaccurate contraindications, and 'parental refusal' (no further details provided).

## Results

A total of 554 children were expected to enter primary school education. Twenty two parents were unavailable for interview and a further 10 children did not have their immunisation status recorded on the central computer. These children were therefore excluded from the study leaving a cohort of 522.

The percentage uptake rates for the cohort were comparable for the published data for the whole health authority for the year 1981 (figures in parentheses). The rates were diphtheria, tetanus, and polio 97·3% (93·0%), pertussis 73·5% (74·7%), and measles 84·8% (83·1%).

No child in the cohort had a recognised DHSS contraindication to diphtheria, tetanus, polio, or measles. Only 12 children (2·3%) would have been excluded from the pertussis immunisation if the current guidelines were used.

'Parental refusal' accounted for the nonvaccination of 2·6% of the cohort for diphtheria, tetanus, and polio, 5% for measles, and 10·7% for pertussis.

Inaccurate contraindications to pertussis and measles were present in 13·4% and 7·5% of the group, respectively. No child failed to receive the other vaccinations on the grounds of inaccurate contraindications. Details of the inaccurate reasons given are provided in tables 1 and 2. The reasons for omitting pertussis which could be accepted using the current guidelines include 'epilepsy' in siblings (n=4), 'epilepsy' in parents (n=4), a reaction to first injection (not defined) (n=3), and an intraventricular haemorrhage in the neonatal period.

Table 1 *Details of reasons given by parents for omitting pertussis immunisation*

| *Reason* | *No* |
|---|---|
| Fits in distant relatives | 20 |
| Family history of atopy | 18 |
| Homoeopathic methods used | 7 |
| Mental retardation in relative | 7 |
| Administrative error | 3 |
| Admission to neonatal intensive care | 3 |
| Febrile convulsion in sibling | 3 |
| Child adopted | 2 |
| Other | 7 |
| Total | 70 |

Table 2 *Details of reasons given by parents for omitting measles immunisation*

| *Reason* | *No* |
|---|---|
| Previous diagnosis of measles | 11 |
| Administrative error | 11 |
| Family history of atopy | 7 |
| Fits in relative | 4 |
| 'Allergic to eggs' | 3 |
| Homoeopathic methods used | 2 |
| Other | 1 |
| Total | 39 |

## Discussion

Eradication of diphtheria, tetanus, polio, and measles from our society is dependent upon many factors, one of which is the comprehensive use of available vaccines.

If we are to achieve effective protection of our population then it is important that a high immunisation uptake rate is achieved and we consequently provide an adequate level of 'herd immunity'. This study shows that if the present DHSS guidelines are correctly applied then less than 3% of children would be excluded from pertussis immunisation and practically none from measles, polio, diphtheria, and tetanus immunisations.

Other workers have attempted to assess the feasibility of improving uptake figures for immunisation. One group found that 7% of children had DHSS contraindications to pertussis and that if parental refusal was taken into consideration an 80% uptake of pertussis immunisation could be achieved.[6] Another study looked at factors which could influence measles uptake and concluded that a 90% uptake was achievable.[3] Neither study obtained their information by direct interview with the parents in the manner encountered in clinical practice.

Inevitably some parents will be antagonistic to the use of any vaccines and so refuse them. Even allowing for this factor this study suggests that it would be possible to achieve uptake rates of 97% for diphtheria, tetanus, and polio, 95% for measles, and 87% for pertussis. It is important to note, however, that the number of children with inaccurate contraindications for both pertussis and measles exceeds the number where parents refused the immunisation. Many of these inaccurate contraindications were ascribed to health professionals.

The reduction in mortality and morbidity from diphtheria, pertussis, tetanus, polio, and measles must continue to be a goal for all involved in the care of children. Uptake figures in excess of those recommended by the World Health Organisation are attainable within the confines of the current DHSS recommendations and contraindications. This, however, is dependent upon a coherent and unified stance on advice and guidance by all health professionals.

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# Cystic fibrosis and renal tubular acidosis

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SUMMARY A case is reported of a child who was born to consanguineous parents and who had the clinical features of two autosomal recessive conditions—cystic fibrosis and distal renal tubular acidosis.

Cystic fibrosis affects 1 in 2000 infants and is the most common inherited disease among white races. The basic metabolic defect is unknown, although chromosome 7 has recently been identified as the site of the defective gene. Increased concentrations of sodium and chloride in the sweat are usually diagnostic of the condition and a defect of chloride reabsorption has been found. When renal function has been examined in cystic fibrosis defects in renal tubular handling of sodium have been found.[1] These have not been associated with clinically recognised abnormalities of renal function.

In contrast, distal renal tubular acidosis is rare. Most cases are sporadic but it may occur in families. The primary defect in distal renal tubular acidosis is a defect in the acidification of urine caused by an inability to generate an adequate hydrogen ion gradient between the blood and tubule fluid. The nature of the cellular defect is unknown but may be a cellular metabolic defect.[2] Similarly, the basic metabolic defect in patients with cystic fibrosis is unknown but the primary defect may be in ion transport.[3]

We describe here the association of distal renal tubular acidosis and cystic fibrosis in the same patient.

## Case report

The patient was a baby girl, the third child of healthy Asian parents of Pakistani origin, who were first cousins. Pregnancy was normal and the birth weight was 3050 g. Her immediate neonatal condition was satisfactory, although she had bilateral talipes equinovarus. There was no family history of either cystic fibrosis or renal tubular acidosis. She had a positive meconium screening test for cystic fibrosis (B M Meconium test) and a low faecal chymotrypsin concentration of less than 10 µg/g (normal range greater than 90 µg/g). A sweat test was arranged at 3 weeks of age, and on the 10th day she was discharged home.

At 13 days of age she was thought to have gastroenteritis and admitted to an infectious disease unit. She was wasted, dehydrated, and acidotic with a pronounced disturbance of the serum concentrations of electrolytes: sodium 128 mmol/l, potassium 2·0 mmol/l, bicarbonate 7·4 mmol/l, urea 13·6 mmol/l, and creatinine 65 µmol/l. She was rehydrated with intravenous fluid and electrolyte replacement but failed to gain weight satisfactorily despite an adequate energy intake and dietary manipulations including a diet free of lactose and cows' milk.

She was transferred to our hospital at 31 days of age for further investigation. The diagnosis of cystic fibrosis was supported by raised concentrations of electrolytes in sweat: sodium 99 mmol/l, and chloride 90 mmol/l, sweat weight – 205 mg) and further low faecal chymotrypsin concentrations. A repeat sweat test also gave abnormal results.

Although adequate oral feeds and electrolytes were given, she failed to gain weight and was dry skinned and dehydrated with pronounced loss of skin elasticity. The urine was not infected but was persistently alkaline (pH 7·5) despite a severe systemic acidosis (pH 7·15), suggesting the diagnosis of distal renal tubular acidosis. Further investigations showed persistent plasma electrolyte abnormalities: sodium 138 mmol/l, potassium 3·1 mmol/l, bicarbonate 10·3 mmol/l, creatinine 45 µmol/l, and a pH of 7·15. At this time urine electrolytes were: sodium 28 mmol/l, potassium 33 mmol/l, bicarbonate 12 mmol/l, creatinine 1·6 mmol/l, and a pH of 7·5. The fractional excretion of bicarbonate was 3·28. Other investigations done at this time were as follows: haemoglobin concentration 146 g/l; white cell count $11\cdot6\times10^9$/l; and platelets $244\times10^9$/l with normal leucocyte morphology. Radiographs of skull and abdomen, and an intravenous pyelogram, were normal. There was no radiological or biochemical evidence of rickets.

The infant was treated with high energy feeds, pancreatic enzyme supplements, prophylactic flucloxacillin, vitamin supplements, and regular chest physiotherapy. The distal renal tubular acidosis was treated with regular oral electrolyte supplements adjusted according to the plasma electrolyte concentrations.

At the age of 7 years she is well and development is normal. Her height of 108·3 cm and weight of 16·4 kg (89% height for age, 70% weight for age, and 88% weight for height) both lie below the third centile. Her electrolyte concentrations are variable, but usually normal with daily oral supplements adjusted on regular electrolyte values. There is no evidence of rickets. The talipes equinovarus has responded to serial splinting and physiotherapy and she walks normally. Her chest radiograph is within normal limits with a Chrispin-Norman score of 3.

## Discussion

Renal tubular acidosis is a syndrome characterised by systemic hyperchloraemic acidosis with inappropriately high urine pH, excessive urinary sodium bicarbonate excretion, and normal glomerular function. In the distal tubular type the urinary pH remains high during severe acidosis (blood pH less than 7·2). In contrast patients with proximal renal tubular acidosis can acidify their urine in severe acidosis, and the complex dysfunction of the proximal tubule characteristic of Fanconi's syndrome is absent. Although there is bicarbonate wastage in distal renal tubular acidosis, it is usually less than 8% of the fraction of filtered bicarbonate, and the acidosis can be corrected with small amounts of sodium bicarbonate.

This child had an inappropriately alkaline urine in the presence of severe acidosis. There is no doubt that she also has cystic fibrosis. The association of these two inherited conditions in the same patient may be a chance finding illustrating the increased occurrence of complex metabolic problems in children of consanguineous marriages. Electrolyte disturbances from a number of causes are common in patients with cystic fibrosis and should be considered in such circumstances. Decreased electrolyte concentrations and profound alkalosis in patients with cystic fibrosis caused by chronic loss of sweat electrolytes and mild gastrointestinal disturbances have been reported.[4] Decreased electrolyte concentrations caused by sweat losses in hot weather have been reported after the original observations by di Sant' Agnese *et al.*[5] In addition to excessive losses both modern low solute milks and breast feeding may lead to an inadequate net electrolyte intake in the infant with cystic fibrosis.[6]

Our patient was unusual because her reduced electrolytes were accompanied by severe acidosis with serum and urinary electrolytes compatible with a profound renal tubular disorder. Finally, in children with an inherited disorder whose parents are first cousins (as are 60% of the Asian population in our area) an additional recessive condition should be suspected if the clinical picture of a disorder is atypical or the response to treatment unsatisfactory.

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# Diffuse nephrocalcinosis and idiopathic renal hypercalciuria

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SUMMARY A 12 year old boy presented with primary nocturnal enuresis. Investigation showed extensive bilateral nephrocalcinosis of no obvious or recognised cause. Persistent severe renal hypercalciuria was confirmed by an intravenous calcium infusion. Idiopathic hypercalciuria is not a common cause of nephrocalcinosis and has not previously been described in a child.

## Case report

A 12 year old boy presented to his general practitioner with primary nocturnal enuresis. His father had a similar problem that resolved at 16 years of age, and an uncle had childhood urinary tract infection and a left duplex kidney. Because of this history an intravenous pyelogram was carried out, which showed extensive renal calcification of medulla and pyramids (fig 1). He was therefore referred to the children's renal clinic for investigations.

Further enquiry elicited that he had always enjoyed good health and had become continent during the daytime at 2 years of age. On direct questioning he admitted to having mild polyuria and polydypsia, but these did not interfere with his daytime activities or sleep at night. On examination he looked well but was mildly obese (height–75th percentile, weight–97th percentile) and showed signs of early puberty (Tanner stage 2). His blood pressure was 130/80 mm Hg. Systemic examination did not show any abnormality.

Results of investigations were as follows (normal ranges in parentheses): haemoglobin concentration 154 g/l; total serum calcium concentration 2·35 mmol/l (2·25–2·60); ionised calcium 1·24 mmol/l (1·17–1·29); inorganic phosphate 1·36 mmol/l (0·80–1·45); albumin 46 g/l (35–50); alkaline phosphatase activity 459 IU/l (<400); plasma sodium concentration 141 mmol/l; potassium 3·8 mmol/l; urea 10·4 mmol/l; bicarbonate 23·5 mmol/l; creatinine 95 μmol/l (42–72); magnesium 0·6 mmol/l (0·6–0·9); and uric acid 0·38 mmol/l (<0·4). Intact serum parathyroid hormone measured by two site immunochemiluminometric assay was 10·8 pmol/l (0·9–5·4). Glomerular filtration rate measured with edetic acid labelled with $^{51}$Cr was 52 ml/minute/1·73 m$^2$ surface area (88–175).

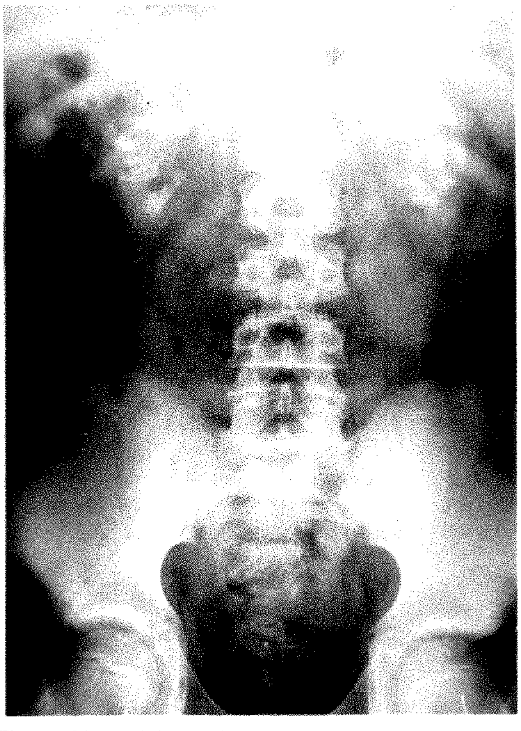

Fig 1 *Plain abdominal radiograph showing extensive renal calcification of medulla and pyramids.*

Urine examination showed no evidence of glycosuria, proteinuria, haematuria, or aminoaciduria. Microscopy of the urine showed no red cells or casts, and culture showed no pathogens. Fasting and postprandial calcium creatinine ratio done on several occasions was between 0·9 and 1·5 mmol/mmol (<0·6). A 24 hour calcium excretion test performed on three occasions, showed calcium excretion of 10·4 to 10·8 mmol/day or 0·2 mmol/kg/24 hours (<0·1 mmol/kg/24 hours). Twenty four hour urine oxalate excretion was 20 to 25 mg/day/1·73 m$^2$ surface area (29–50). These results were confirmed by a reference laboratory. Following treatment with ammonium chloride (0·1 g/kg body weight), urinary pH dropped to 5·4 at five hours, and 5·3 at six hours. Ultrasound examination of the kidneys confirmed extensive nephrocalcinosis but also showed in addition cortical calcification to the medulla. Radiography of the left hand and wrist showed no abnormality.

Oral hydrochlorthiazide 1 mg/kg for two months failed to influence his calcium excretion. Intravenous infusion of calcium gluconate (1·25 mg/kg over 35 minutes showed suppression of intact serum parathyroid hormone (fig 2). Although there was no significant rise in the serum calcium concentration there was a significant increase in calcium excretion in the urine. There was no evidence of hypercalciuria in first degree relatives.

## Discussion

The three most frequent causes of generalised nephrocalcinosis are hypercalcaemia, defects in urine acidification, and hyperoxaluria.[1] Familial juvenile nephronophthisis or medullary cystic disease may show some degree of nephrocalcinosis and hypercalciuria. The other rare causes include treatment with diuretics, Bartter's syndrome, and hypomagnesaemia. Idiopathic hypercalciuria is a common condition. Most cases are asymptomatic,

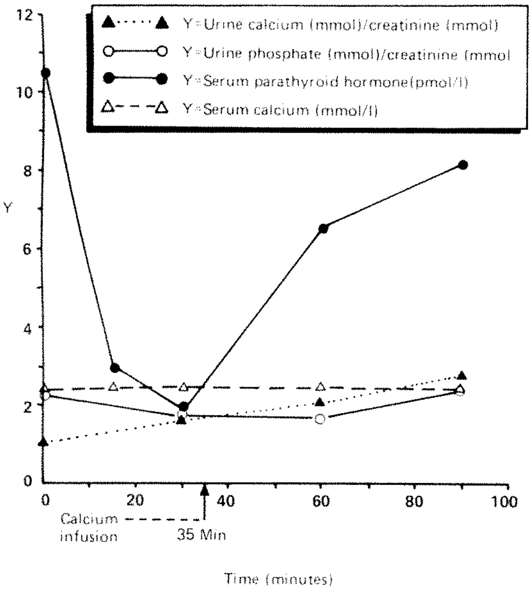

Fig 2 *Calcium loading test showing calcium infusion (1·25 mg/kg body weight) given over 35 minutes that suppressed high parathyroid hormone concentrations and although there was no appreciable rise in serum calcium, urine calcium excretion increased significantly.*

some of them present with persistent or recurrent haematuria,[2 3] or urolithiasis.[4] Recently many other urinary tract disorders[5] such as dysuria, frequency, and enuresis have been described secondary to idiopathic hypercalciuria, but in these cases the threshold for diagnosing hypercalciuria is rather low. Diffuse nephrocalcinosis caused by idiopathic hypercalciuria has not been described.

All the known causes of generalised nephrocalcinosis have been excluded and the diagnosis of familial juvenile nephronophthisis or medullary cystic disease are unlikely considering the clinical presentation and severity of nephrocalcinosis. In our case it was shown that hypercalciuria is caused by a renal tubular leak as both fasting and postprandial urine samples showed excessive calcium excretion, and on calcium infusion urine calcium excretion increased tremendously, although serum concentrations did not rise appreciably. Intact serum parathyroid hormone concentrations may be raised secondarily in idiopathic renal hypercalciuria[6] as a reflection of the urinary calcium leak, and they can be suppressed by calcium loading, which was also shown in this case by the calcium infusion test. Hydrochlorthiazide can suppress calcium excretion in cases of idiopathic hypercalciuria but it is effective in only about 70% of cases. In this case it seems both conditions were related and hypercalciuria is not simply an epiphenomenon. The problem of nocturnal enuresis has been successfully managed by toilet training and at present the patient has been advised to take a low sodium and high fibre diet hoping to decrease hypercalciuria and hence avoid further renal damage. During the period of follow up (eight months) he has remained healthy although his renal function is deteriorating slowly.

We would like to thank Dr P Lucas, Lecturer in Renal Medicine, for his help and Miss J Cook for secretarial help.

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# Generalised lymphangiomatosis with chylothorax

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SUMMARY A 9 month old boy presented with acute respiratory distress and was found to have a left pleural effusion. The chylous nature of the effusion, multiple bony lytic lesions, and splenic cysts lead to the diagnosis of congenital lymphangiomatosis with chylothorax. Surgical intervention including pleurectomy was required after unsuccessful conservative management.

Chylothorax is rare in children. More than half of the cases occur as a complication of cardiothoracic surgery. It has been observed as a benign self limiting phenomenon in neonates. Chest trauma and thoracic malignancy account for most of the remaining cases. A case of chylothorax with lytic bony lesions due to lymphangiomatosis is described.

## Case report

A 9 month old white boy presented with a three day history of tachypnoea. He was one of dizygotic twins born by caesarean section at 38 weeks' gestation weighing 3000 g. He was breast fed initially and was on solids and artificial milk at presentation. Family history was non-contributory.

On examination, although tachypnoeic at 72 breaths/minute with subcostal recession and nasal flaring, he was playful. He was pink in air and not feverish. A carinatum deformity was observed. Examination suggested a large left pleural effusion with contralateral mediastinal shift. Small bluish macules were observed on the back.

Chest radiography (fig 1) confirmed a large left sided effusion and revealed lytic lesions in the head of the left humerus and anterior end of several ribs. Skeletal survey showed lytic lesions in the left femur (fig 2). Sonography confirmed the pleural effusion and showed multiple cystic lesions in a slightly enlarged spleen. A computed tomogram of the chest did not add further information and a bone scan was normal. The liver was normal and there were no other features of abdominal malignancy or lymphadenopathy.

Initial blood count and concentrations of serum urea and electrolytes were normal and blood and urine cultures sterile. Total serum protein concentration was 46 g/l with serum albumin of 26 g/l. Iliac crest marrow aspiration and bone trephine were normal. Thoracocentesis relieved the respiratory distress and was followed by dramatic resolution of clinical signs. It yielded 330 ml of turbid pink fluid which was subsequently identified as chyle (protein 45 g/l, cholesterol 2·6 mmol/l, and triglyceride 8·8 mol/l). Microscopy showed white cells in abundance, 98% of which were mature lymphocytes. Culture was sterile.

Rapid reaccumulation of the effusion necessitated continuous pleural drainage. A low fat medium chain triglyceride diet was commenced. Surgical evaluation was felt necessary due to a continuous loss of 300 ml of chyle daily requiring multiple plasma and albumin transfusions. A loss of one kilogram in weight, hyponatraemia, hypoalbuminaemia, and lymphopaenia had supervened in the two weeks since presentation. At thoracotomy a diffuse welling of chyle was observed from the anterior and superior mediastinum as well as from both the thoracic duct and an enlarged accessory duct. Both ducts were ligated and pleurectomy performed.

On histological examination a specimen of the pleural tissue and from a bone biopsy showed

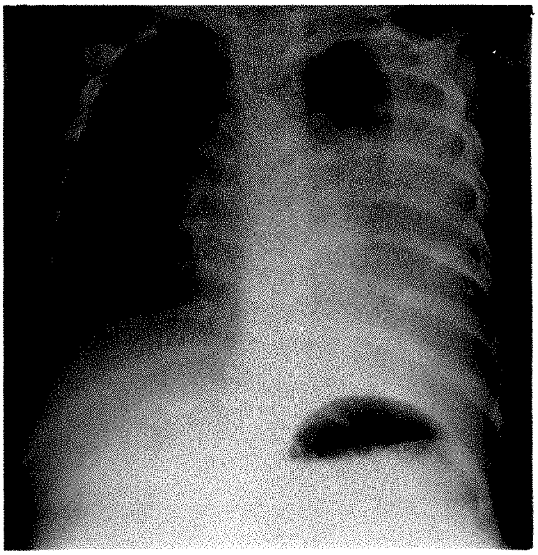

Fig 1 *Chest radiograph of patient.*

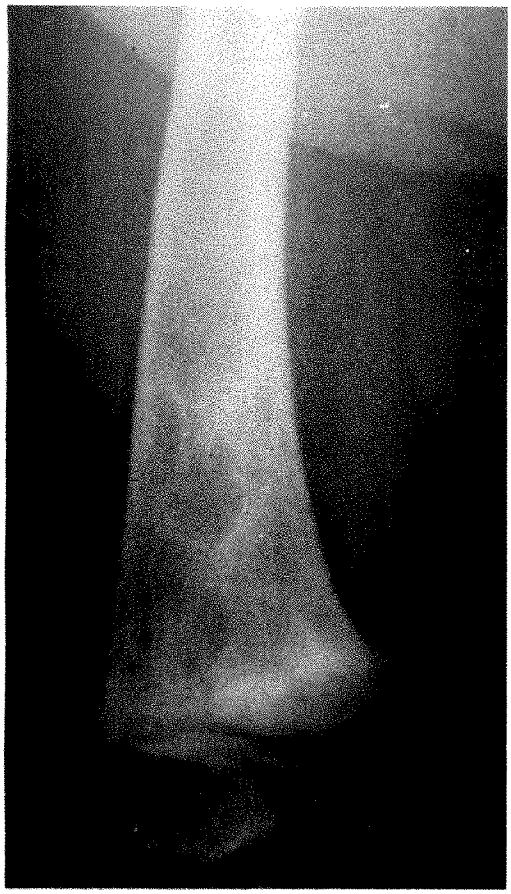

Fig 2 *Radiograph of left femur showing lytic lesions.*

numerous small endothelial lined lymphatic vessels consistent with general lymphangioma. A biopsy specimen of a skin lesion was normal.

Apart from a left Horner's syndrome, postoperative recovery was uneventful. Five months after his initial presentation he developed clinical and radiological reaccumulation of the left pleural effusion. A chest drain was inserted and it continued to drain about 300 ml of chyle per day. Twelve days later he underwent a second thoracotomy. The left lung was found densely adherent to the chest wall but pockets full of blood stained fluid were also present. Two ribs had been eroded and destroyed. Decortication of the left lung was performed. The effusion reaccumulated slowly over the next 10 days but responded to tetracycline pleurodesis. Three months after the second thoracotomy he was well. As yet no asymmetry of chest development has been observed.

## Discussion

Berberich *et al* described a 3 year old child with bilateral chylous pleural effusions, multiple bone lytic lesions, and pathological fracture of the tibia.[1] They reviewed five previously reported cases with congenital lyphangiomatosis of bone with chylothorax. Since then three other cases have been reported.[2–4] The age at presentation ranged between 9 months and 17 years. The most common presenting symptom was respiratory distress. Four of the nine cases presented with bilateral pleural effusions.[1 4] Four patients developed right sided chylothorax after initial presentation with a left effusion,[1 2] and in one patient the chylothorax was confined to the left pleural cavity.[3] In all cases bony lytic lesions were an incidental finding. All but one of these cases occurred in boys.[1] Two patients developed pathological fractures,[1] and one had associated chylopericardium.[3] In no previous report was splenic involvement diagnosed antemortem, although most of the cases in the literature date from the presonographic era. In the current case, however, it was the detection of multiple 'splenic cysts' and the presence of bony lytic lesions that led to a radiological diagnosis of lymphangiomatosis.

Management of these patients remains speculative but it is notable that both cases managed conservatively died whereas only one of the seven managed surgically succumbed.[1] It has been concluded recently that conservative management in the form of chest drainage and low fat diet is successful in most cases of childhood chylothorax.[5] Most of the cases reviewed, however, followed cardiothoracic surgery.[5] Conservative management usually involves a low fat intake supplement with medium chain triglycerides, which are absorbed directly into the portal venous system without forming chylomicrons.[6] In one report the chylothorax resolved after intrapleural instillation of 50% dextrose.[3] In another case reviewed the chylothorax was apparently due to an intrathoracic collection of lymph from a rib lesion and resolved after resection of the rib.[1]

This review of cases of chylothorax with lymphangiomatosis lends support to a recent suggestion that when there is evidence of an underlying lymphatic disorder, this is an indication for earlier rather than later surgical intervention.[5] Surgery usually involves ligation of thoracic duct and accessory lymphatic channels, thoracotomy, and lung decortication.[1 4]

We acknowledge the help of Dr M Liberman and Dr R Dinwiddie with the management of this case and the preparation of this report.

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# Multiple nerve palsies in β thalassaemia major

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SUMMARY A patient with β thalassaemia major is described who developed a lower motor neurone facial nerve palsy on the left side, together with a phrenic nerve palsy on the same side, during the course of the illness. This complication has not been reported before in haemoglobinopathies.

β thalassaemia major is the commonest haemoglobinopathy found in Sri Lanka. Neurological complications have been described in thalassaemia but these are mostly confined to spinal cord compression due to extramedullary haematopoiesis[1–3] and auditory nerve involvement.[4]

## Case report

An 11 year old Sinhalese girl, who developed pallor together with progressive abdominal distension during the latter half of infancy, was diagnosed as a case of β thalassaemia major after relevant haematological investigations. She was the youngest in a family of five children and the other siblings were in good health. There was no history of consanguinity and the father had died of ischaemic heart disease at 50 years of age. From late infancy onwards she received numerous blood transfusions at infrequent intervals due to poor compliance. The aim was to maintain the haemoglobin concentration above 80 g/l. Only a few doses of desferrioxamine were given to her because it was not readily available.

At the age of 7 years she developed a classical left lower motor neurone facial palsy that did not resolve with time. There was impairment of taste in the anterior part of tongue but no hyperacousis. There was no evidence of middle ear infection or mastoiditis. Audiometry was normal. She developed corneal scarring due to exposure keratitis and a tarsorrhaphy was performed to minimise further damage to the cornea. At 7½ years of age she was admitted with severe pallor and congestive cardiac failure. A chest radiograph showed an elevated left dome of the diaphragm. Fluoroscopic screening confirmed paralysis of the left dome. The rest of the neurological examination, including funduscopy, was normal. At 9 years of age, as her splenic size had increased to 15 cm below the left costal margin and the transfusion requirements had increased, a splenectomy was performed. Since then she has been on monthly prophylactic benzathine penicillin treatment.

At present both her height and weight are below the 3rd centiles, she is normotensive, and has the typical thalassaemic facies. Her liver span extends 13 cm below the right costal margin. The most recent investigations were as follows: haemoglobin concentration 85 g/l; white cell count $10{\cdot}5\times10^9$/l with polymorphs 55%, lymphocytes 35%, monocytes 3%, eosinophils 6%, and basinophils 1%; reticulocyte count $0{\cdot}4\times10^{-3}$/l. The peripheral blood picture showed hypochromic and microcytic red cells, pronounced anisocytosis, normoblasts, hypersegmented neutrophils, and few macrocytes; platelet count $290\times10^9$/l; alkaline denaturation test positive; haemoglobin electrophoresis showed adult haemoglobin 15% and fetal haemoglobin 85%. Radiographs of the hand showed rectangular metacarpals with reticulation and a radiograph of the skull showed widening of diploe with 'hair-on-end' appearance. Radiographs and serial tomograms of the cervical and thoracic spine did not show any paravertebral soft tissue shadows. Consent for a myelogram was refused.

## Discussion

Neurological complications in thalassaemia are rare. Extramedullary haematopoiesis is well recognised in thalassaemia at sites such as the liver and the spleen. Rarely such haematopoietic tissue may be found within the spinal canal, extradurally, causing compression of the spinal cord.[1-3] Infrequently, infiltration of the middle ear by haematopoietic tissue may lead to hearing loss.[4] These complications are more common on a low transfusion regime because it leads to bone marrow hyperplasia with widening of bones and extramedullary haematopoiesis.[3] This patient was on a low transfusion regime due to poor compliance and had radiological evidence of widening of bones.

The commonest cause of an isolated unilateral lower motor neurone facial nerve palsy at this age is Bell's palsy; however, in about 85% of cases, resolution occurs with time. Absence of evidence of middle ear infection, or a vesicular eruption around the external auditory meatus at the time of the facial palsy, excludes otitis media and herpes zoster as likely causes. Poliomyelitis or another enteroviral infection as a potential cause is unlikely in this patient as she had received appropriate doses of oral polio vaccine in the past and also because the two nerve lesions were spaced out in time. Therefore, the probable cause for the facial nerve palsy is pinching of the nerve at one of the narrow points along its course, such as within the facial canal, due to widening of diploeic bone. The radiological evidence of widening of skull diploe supports this hypothesis, although an unresolved Bell's palsy cannot be conclusively ruled out.

The reason for the phrenic nerve palsy is more difficult to explain. It may have been due to pressure from a small paravertebral mass of haematopoietic tissue. Although irradiation has been used successfully to treat paravertebral masses,[2] it could not be used in this patient because exact localisation was not possible.

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# Betaine for treatment of homocystinuria caused by methylenetetrahydrofolate reductase deficiency

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SUMMARY A 24 day old girl with homocystinuria and hypomethioninaemia caused by methylenetetrahydrofolate reductase deficiency presented with rapidly progressing encephalopathy and myopathy. An almost complete recovery was achieved by treatment with betaine.

5,10-Methylenetetrahydrofolate reductase (MTHFR) deficiency[1] leads to deficient remethylation of homocysteine and is one of the causes of homocystinuria (figure). The other causes of homocystinuria are defects in cobalamin metabolism or deficient cystathionine β-synthase activity.

Methionine accumulates with homocystine in cystathionine β-synthase deficiency,[1] whereas in patients with disorders in cobalamin metabolism or with MTHFR deficiency methionine synthase is functionally deficient and the increased concentration of homocystine occurs with normal or decreased methionine concentrations. In the latter conditions neurological impairment is the most important clinical finding. When symptoms occur in early infancy there is often rapid deterioration with respiratory failure.

Methylmalonic aciduria or macrocytic or megaloblastic changes of the bone marrow, or both, usually occur with homocystinuria in patients with disorders of cobalamin metabolism. These condi-

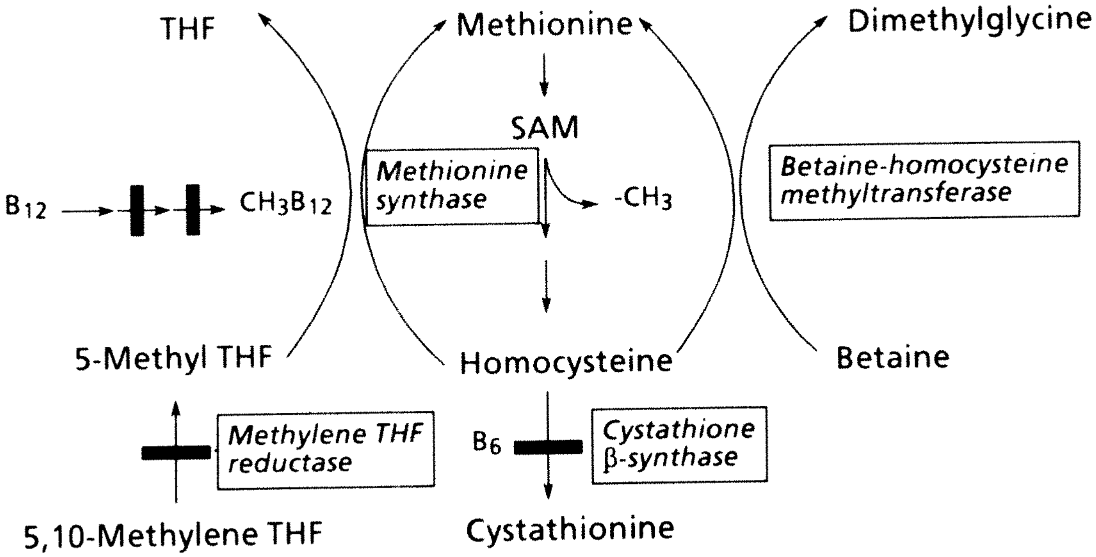

Figure *Metabolic pathways of homocysteine. Sites of metabolic defects leading to homocystinuria are indicated by blocks. SAM=S-adenosylmethionine; THF=tetrahydrofolate;* $B_{12}$*=cobalamin; and* $B_6$*=pyridoxal 6-phosphate.*

tions usually respond to high doses of hydroxocobalamin. In MTHFR deficient patients, treatment with folate or cobalamin does not increase the methionine synthase activity as shown by the poor biochemical and clinical response.[2]

The alternative to the methyltetrahydrofolate dependent remethylation pathway of homocysteine is the betaine dependent pathway (figure). Treatment with betaine was efficient in lowering homocystine concentrations and reduced methionine concentration to normal in a 2 year old child with MTHFR deficiency.[3] The child was microcephalic and severely retarded when the betaine treatment was started, and the clinical response was limited. Two other patients treated with betaine have been reported (NJ Brandt, *et al.* Treatment of methylenetetrahydrofolate reductase deficiency from the neonatal period. Presented at the Society for the Study of Inborn Errors of Metabolism Annual Symposium, Amersfoort, The Netherlands, 1986). One was diagnosed prenatally. Betaine was started at the age of 2 weeks before any symptoms had appeared, and at the age of 15 months psychomotor development was normal. In the other child, treatment was started 27 days after the onset of symptoms at the age of 36 days. There was 'considerable developmental improvement' by 12 months of age. Two infants who died after 4 days and after 3 weeks of treatment have also been mentioned in a review.[2] We now report an infant in whom successful treatment with betaine was started at the age of 7 weeks after a period of three weeks during which there was rapid progressive neurological deterioration.

## Case report

A baby girl, the first child of healthy parents who are cousins with no family history of neurological, psychiatric, or thrombovascular disease, was born after a normal pregnancy. Vacuum extraction was used because of slow progression of the delivery. Apgar scores were 4, 5, and 8 at one, five, and 10 minutes. The birth weight was 3030 g and the head circumference 34 cm. Mild respiratory distress lead to two days treatment in an incubator. At 6 days of age the child was discharged from hospital. She was breast fed and remained healthy until 24 days of age, when she had an attack of cyanosis and unconsciousness. On admission she was pale, hypotonic, and lethargic. Blood glucose and serum electrolyte concentrations, acid base balance, and analysis of cerebrospinal fluid were normal. The haemoglobin concentration was 136 g/l. C reactive protein concentration was less than 10 mg/l.

Electrocardiogram and chest radiograph were normal. Two electroencephalograms obtained during the first week after admission were normal, although weak muscular twitching, tongue fasciculation, and seizures developed.

A positive urinary nitroprusside reaction was found two days after admission. Quantitative amino acid analysis by ion exchange chromatography showed a high plasma homocystine concentration and no detectable methionine. Increased urinary excretion of homocystine and cystathionine were also found. Urinary organic acid excretion analysed by gas chromatography and mass spectrometry was normal. The bone marrow morphology was normal. Plasma cobalamin and erythrocyte folate concentrations were also normal.

Treatment with pyridoxine (100–150 mg/day), hydroxocobalamin (1 mg/day), and folic acid (30–60 mg/day) was started. There was no response to the treatment, her clinical condition deteriorated rapidly, and respiratory failure necessitated assisted ventilation on the 21st day after admission. The electroencephalogram was then abnormal showing abundant spike and wave potentials. After three days of artificial ventilation betaine (3 g/day) and methionine (0·5 g/day) were given orally. After two days of treatment the muscular tone improved, and after two weeks there was no further need for assisted ventilation. The homocystine concentrations in urine and plasma decreased below the detection limit and a normal plasma methionine concentration was obtained without methionine supplementation (table). The electroencephalogram returned to normal, and she caught up in growth and psychomotor development.

MTHFR deficiency was established by measurements in cultured skin fibroblasts as described by Mudd *et al.*[4] The activity found was 0·34 nmol/(hour×mg protein). The mean activity in five controls was 15·5 nmol/(hour×mg protein) (range 9·0–32).

Total plasma homocysteine concentration—that is, the combined free and protein bound fractions, was 78 μmol/l (reference interval in adults 4·2–17·8 μmol/l) at the age of 9 months, when she was taking 3 g betaine daily. The daily intake of betaine was then increased to 6 g daily. The effect on total homocysteine concentration was limited; after two months total homocysteine concentration had only decreased to 70 μmol/l, but the plasma methionine concentration though still within the normal range, had increased.

Mainly because of persisting feeding difficulties the child was kept in hospital until the age of 5 months. When last seen at the age of 12 months the increments of length, weight, and head circumference were normal, following the 50th, 25th, and 10th percentiles, respectively. Her psychosocial behaviour was normal but her motor development was retarded by two to three months.

## Discussion

Methylenetetrahydrofolate reduction is the first step in the biosynthesis of methyl groups, which—through homocysteine methylation and S-adenosylmethionine formation—participate in phospholipid biosynthesis and RNA and DNA modification, among other things.

As shown by the return to normal of plasma and urinary methionine and homocysteine concentrations in our case as in others, (NJ Brandt, *et al.* Treatment of methylenetetrahydrofolate reductase deficiency from the neonatal period. Presented at the Society for the Study of Inborn Errors of Metabolism Annual Symposium, Amersfoot, The Netherlands, 1986),[2–3] exogenous betaine can supply methyl groups for homocysteine methylation. The accompanying clinical recovery in our case indicated that the metabolic derangement (presumably a shortage of methyl groups) responsible for the neurological symptoms was corrected by betaine treatment. Thus is is imperative to recognise these patients early so as to start treatment before irreversible damage has occurred.

Table *Clinical and biochemical responses to different treatments*

| | *Age (weeks)* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *4* | *5* | *8* | *9* | *21* | *29* | *36* |
| | *Deterioration* | | *Improvement* | | | | |
| Treatment: | | | | | | | |
| Pyridoxine, hydroxocobalamin | No | Yes | Yes | Yes | Yes | No | No |
| Folic acid | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Methionine 500 mg/day | No | No | Yes | No | No | No | No |
| Betaine 3 g/day | No | No | Yes | Yes | Yes | Yes | Yes |
| Plasma methionine concentration (μmol/l) | <10 | <10 | 395 | 15 | 18 | 18 | 18 |
| Plasma homocystine concentration (μmol/l) | 15 | 30 | <10 | <10 | <10 | <10 | <10 |
| Urinary homocystine concentration (mmol/mol creatinine) | 230 | 140 | — | 18 | 17 | <10 | <10 |

To ensure long term health, betaine should if possible be given in doses high enough to return total plasma homocysteine concentration to normal, as even a moderate increase in a possible risk factor for thrombovascular disease.[5]

We thank Dr B Hultberg, Department of Clinical Chemistry, University of Lund, for determining the total plasma homocysteine concentrations. This study was supported by grant 13X-585 from the Swedish Medical Research Council and the KSS Paediatric Research Foundation.

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## *Special report*

# Management of asthma: a consensus statement

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SUMMARY In developing these international guidelines there were several unifying themes in the diagnosis and simple management of childhood asthma. For the purposes of the meeting, asthma was operationally defined as 'episodic wheeze and/or cough in a clinical setting where asthma is likely and other rarer conditions have been excluded'.

In making a diagnosis of asthma, a full history is a prerequisite. Additional tests are only used to support clinical impression and to provide objective evidence for therapeutic recommendations. General features of a multidisciplinary approach include an appreciation of the importance of psychosocial factors, counselling, and education. Drugs should be prescribed in a rational sequence: $\beta_2$-stimulants for mild episodic wheeze; sodium cromoglycate for mild to moderate asthma; inhaled steroids for moderate to severe asthma; with xanthines, ipratropium bromide, and oral steroids having their place in more persistent and severe cases.

Children and their parents should be reassured that if asthma is properly controlled there is no reason why the child should not lead a normal and physically active life. The management of asthma is rewarding and return to 'normal' lifestyle is nearly always possible with active participation in sporting activities.

Asthma affects more than 10% of children with a suggestion that prevalence, severity, and mortality has increased in recent years. At the same time there has been a considerable increase in prescribed treatment and hospital admissions for the disease. This is unnecessary as most patients are easily diagnosed and treated. Yet asthma remains commonly underdiagnosed and under treated.

Increased understanding of the pathology of the condition has allowed us to make more rational decisions about therapeutic schedules. Delivery systems for inhaled preparations have improved considerably to facilitate administration even to small children. This paper represents an international agreed policy which should be of value to paediatricians and general practitioners in providing a sound basis for the diagnosis and management of childhood asthma. It is divided into sections to account for the differences between children of different ages. The protocols are outlined in the text and in simple algorithms. To facilitate a pragmatic approach to the condition, asthma is defined as 'episodic wheeze and/or cough in a clinical setting where asthma is likely and other rarer conditions have been excluded'.

## Diagnosis of asthma in children unable to perform lung function tests (fig 1)

The use of the label 'asthma' in older children has important clinical consequences. It implies a syndrome consisting of chronic or recurrent wheezing and/or coughing with recognisable variable airway obstruction responsive to a limited range of effective treatments. In children under 5 years, however, we can be neither so confident that wheezing is equivalent to asthma, nor that there is a homogeneous underlying pathogenesis, even in those children who do not have an alternative diagnosis. Even when we confidently make a diagnosis of asthma, the response to treatment is often unsatisfactory in the youngest age group. A number of these controversial points need to be addressed in considering a scheme for the diagnosis of asthma in this age group.

A variety of synonyms have been used to describe asthma in young children (wheezy bronchitis, wheeze associated respiratory infection, infantile asthma, etc). Behind each is the implication that we can recognise variable intrathoracic airway obstruction by means of the clinical feature of recurrent wheeze. Recurrent night cough, and to a lesser

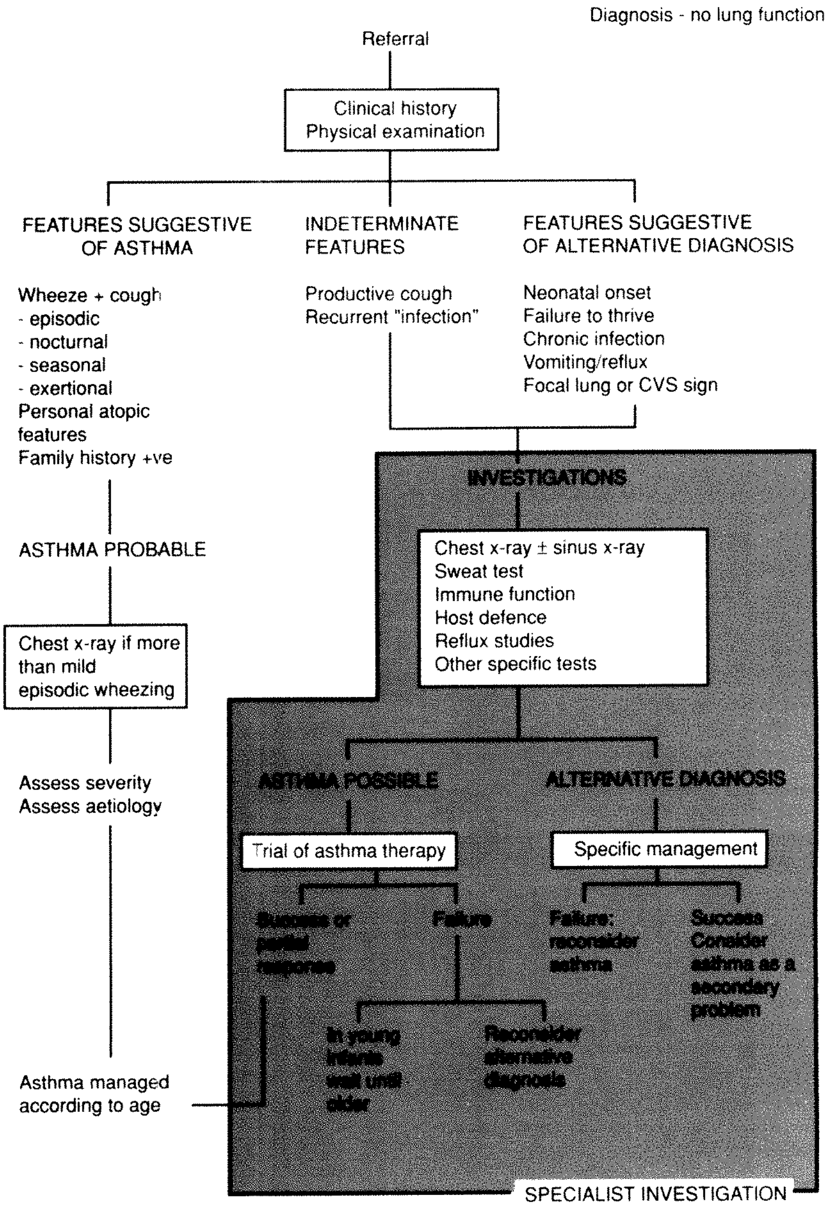

Fig 1 *Diagnosis of asthma in children unable to perform lung function tests. CVS=cardiovascular system.*

extent, recurrent spasmodic croup, have also been felt to be features associated with infantile asthma, the implication being that they all result from some degree of irritability of the intrathoracic airways.

There are probably at least two patterns of asthma in infancy. On the one hand there are infants who develop recurrent episodes of wheeze associated with acute viral infections, who come from non-atopic backgrounds, and outgrow their symptoms over the preschool years. On the other hand, there are children with asthma and an atopic background, often associated with eczema and a strong family history, who develop symptoms slightly later in infancy which persist until later in childhood. It may not be possible to distinguish the two patterns of asthma in individual children. However, the term asthma encompasses these extremes.

Asthma is not an all or none diagnosis at any age. There is a range of severity in the population, from entirely normal at one extreme, to severe persistent wheezing at the other. No test, question, or physical sign can provide a precise cut off point. The same limitations apply to the diagnosis of asthma in preschool children.

Wheeze is a feature of intrathoracic airway obstruction. For instance, bronchial stenosis, tracheobronchomalacia, and cystic fibrosis can cause recurrent or persistent wheeze indistinguishable from non-structural, non-focal airways obstruction (that is, asthma). Although wheeze is not synonymous with asthma, asthma is common and alternative diagnoses are rare.

As wheezing in infancy is common, it is quite clear that on occasions children with other diseases (for instance cystic fibrosis or congenital heart disease) will also suffer from asthma. From a practical point of view it is important to recognise that recurrent wheeze in one of these conditions implies the need for a trial of some form of antiasthma treatment such as bronchodilators.

The diagnostic scheme starts with a full clinical history and physical examination. Some features strongly support a diagnosis of asthma, while others are indeterminate or suggestive of alternative diagnoses. There are no definitive diagnostic tests. A chest radiograph should be taken in severe or unusual cases to exclude foreign body and secondary or structural lung disorders such as congenital anomalies. Allergy tests may help in assessing aetiology after a diagnosis has been made. The final diagnostic criterion is a trial of appropriate asthma therapy. When an alternative diagnosis is suspected, (for example, cystic fibrosis, recurrent aspiration, or a disorder of host defences) the patient should be referred to a paediatric respiratory physician for specialist investigation and management.

## Diagnosis of asthma in children able to perform lung function tests (fig 2)

The current approach to support the diagnosis is to assess lung function data both at rest and after challenge, and to combine these data with results from allergy tests. A clinical history must be taken with attention to personal, family, and environmental features. A symptom diary is a useful adjunct to clinical history. In most cases, the diagnosis will be obvious at this stage, but lung function data, at rest and after challenge, can be used to support the diagnosis in doubtful cases.

Children from the age of 5–6 years onwards are usually able to perform simple lung function tests such as peak flow rate and forced expiratory volume in one second ($FEV_1$). More sensitive techniques are generally restricted to specialist centres. Spirometry and flow volume loop measurements, though not essential for a diagnosis of asthma, are useful for differential diagnosis and for the monitoring of patients with severe asthma.

Simple lung function tests can be used to support a diagnosis of asthma in three ways: (1) considerable variability of peak flow rate or $FEV_1$ over short periods of time, for instance during home monitoring. Excessive variability can be defined as a fall of at least 20% from the established maximum for any individual child. (2) Improvement of at least 20% in peak flow rate or $FEV_1$ after administration of an inhaled $\beta_2$-stimulant. (3) Decrease of 20% or more in peak flow rate or $FEV_1$ after bronchial challenge. The diagnosis of asthma is hampered in cases of consistently abnormal lung function (that is, no change with bronchodilators or with provocation). In special cases a therapeutic trial of oral steroids may be needed to assist diagnosis.

Bronchial hyper-responsiveness is considered a key feature of asthma. It can be shown in a number of non-asthmatic conditions, however, such as transiently with viral infection, environmental pollution, smoking, atopic dermatitis, and cystic fibrosis. Hyper-responsiveness may also occur in healthy children and conversely asthmatic children may occasionally have no demonstrable hyper-responsiveness.

Exercise is the easiest challenge to perform in the clinic. Of the more sensitive bronchial challenge tests, methacholine is the easiest and least expensive test, whereas histamine is the best standardised. Non-pharmacological challenge tests may either require expensive equipment and maximal patient cooperation (cold air challenge) or are not yet adequately standardised (ultrasonically nebulised distilled water).

The contribution of allergy testing to the diagnosis

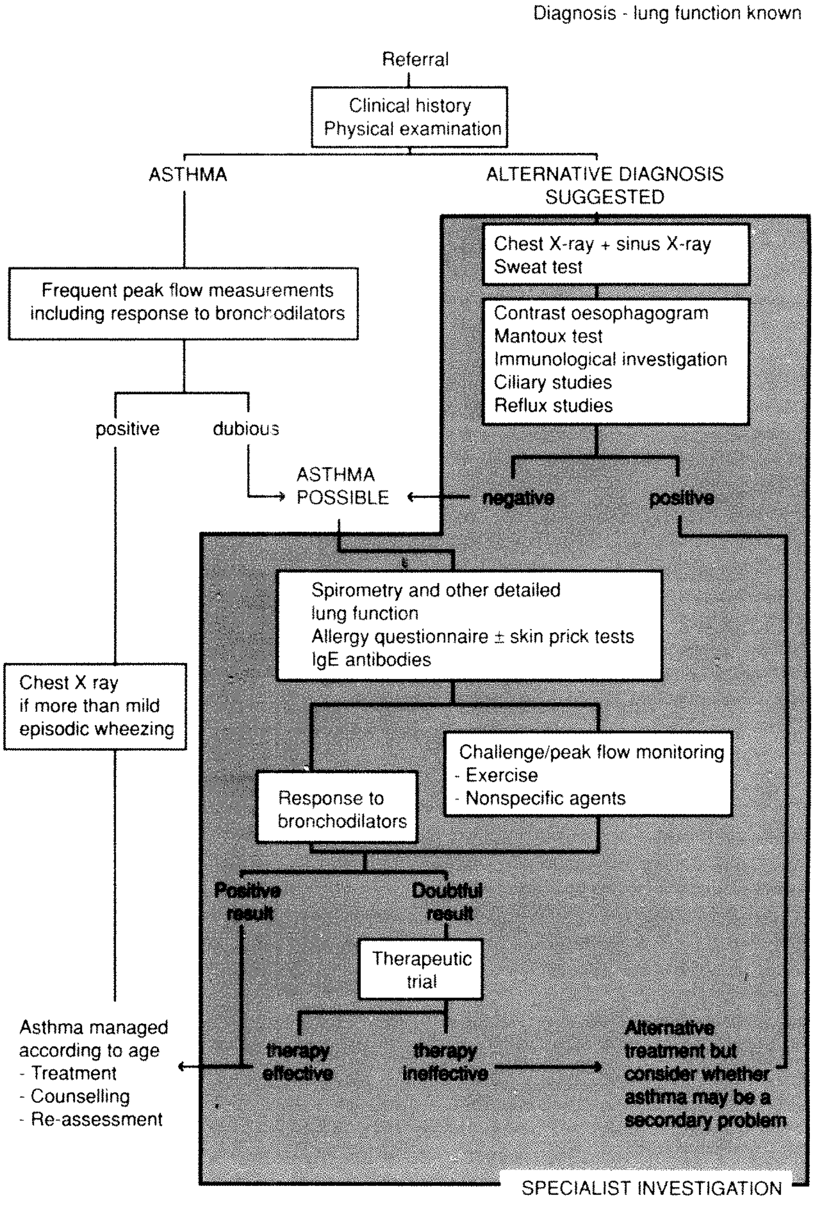
Diagnosis - lung function known
Referral
Clinical history
Physical examination
ASTHMA
ALTERNATIVE DIAGNOSIS SUGGESTED
Chest X-ray + sinus X-ray
Sweat test
Contrast oesophagogram
Mantoux test
Immunological investigation
Ciliary studies
Reflux studies
Frequent peak flow measurements including response to bronchodilators
positive
dubious
ASTHMA POSSIBLE
negative
positive
Spirometry and other detailed lung function
Allergy questionnaire ± skin prick tests
IgE antibodies
Chest X ray if more than mild episodic wheezing
Challenge/peak flow monitoring
- Exercise
- Nonspecific agents
Response to bronchodilators
Positive result
Doubtful result
Therapeutic trial
therapy effective
therapy ineffective
Asthma managed according to age
- Treatment
- Counselling
- Re-assessment
Alternative treatment but consider whether asthma may be a secondary problem
SPECIALIST INVESTIGATION

Fig 2 *Diagnosis of asthma in children able to perform lung function tests.*

and management of childhood asthma remains controversial. Skin prick tests and/or total IgE concentration may be useful in some children to reinforce a possible diagnosis and indication of causes of asthma. Specific (allergen) bronchial challenges will rarely be required and carry the risk of prolonged late reactions and enhanced bronchial hyper-reactivity. Often the choice of treatment is made irrespective of the results of testing. Nevertheless there are coherent arguments for the determination of offending allergens in order to counsel patients about avoiding specific triggers.

Establishing the diagnosis of asthma is usually straightforward and is supported by lung function studies. However, a therapeutic trial may be necessary to make a final diagnosis.

## Common management strategies in children of all ages

The management goals common to all age groups are to reduce symptoms and optimise lifestyle with few limitations on activity at home, school, work, and leisure, utilising treatments with a low incidence of side effects. This should prevent development of asthma related emotional disorders, avoid hospitalisation, and reduce morbidity and mortality. By the reduction of hyper-responsiveness and the restoration of normal lung function, the prevention of irreversible airway obstruction may be possible.

### ENVIRONMENTAL MANIPULATION

Most children over the age of 5 with asthma have clear evidence of allergy. Precipitating trigger factors should be identified and parents and children counselled on avoidance where possible. There is overwhelming evidence that smoking produces a rapid reduction in lung function. Therefore the avoidance of cigarette smoke must be a priority. House dust mite, the commonest allergen, is difficult to remove but the following measures are helpful: use of plastic mattress covers and pillow cases; removal of feather bedding, bedroom carpet, and soft toys from the bed; and regular vacuum cleaning. If there is convincing evidence of allergy to the family pet it should be removed but if so it will take at least three months for the dander to be totally eliminated from house dust. Exposure to seasonal pollens can be reduced by keeping windows closed during the day and by installing air conditioners and/or air filters, but further work is required to establish their efficacy. In children, asthma is rarely precipitated by food or drink, but if so, avoidance is indicated. Asthma may be exacerbated by emotional disturbance and asthma control can be compromised by adverse psychosocial factors. Psychotherapeutic management is for the most part simple explanation of the condition but various psychotherapeutic approaches have been shown to be of value as an adjunct to standard drug treatment.

### ASSESSMENT OF BASELINE SEVERITY

Before treating, it is essential to assess lung function at baseline and after full doses of $\beta_2$-stimulants to determine what improvements in airflow are possible. Symptom severity should be continually reassessed during treatment. Are the symptoms truly intermittent or do they regularly interfere with sleep, sport, or other activities? Progress can be monitored by diary card record of symptoms. Measurements of peak flow rate should be implemented regularly. Frequency of use of rescue treatments such as $\beta_2$-stimulants should be assessed. More sophisticated lung function tests may be necessary for differential diagnosis and for monitoring severe asthma and its management.

### SELF MANAGEMENT

An essential aim for the management of asthma should be to train the child and/or the parents to become an effective first line in the management of symptoms and attacks so that they can cope with most of them without immediate recourse to a doctor, but also to have clear guidelines on when it is necessary to seek medical help. For small children the parents will make all the first line management decisions, but this responsibility will pass more and more to the child as adolescence approaches. They should have ready access to medical advice if long term control is poor and for acute severe attacks. Achieving this management aim necessitates instruction of the patient and parents in the use of drugs and apparatus required for asthma control. The management of asthma should be an example of 'shared caring' in which the child, the parent, and the medical advisors act as a team in managing the asthma. Information, including instructions about medication, is most conveniently given in written form so that it can be referred to from time to time. Benefit is derived from self management programmes or education packages in which children are given the same information as parents, but at an appropriate level. Such a package enables the child to recognise signals and so make decisions about self referral (to parents or doctor), self medication, and the avoidance of precipitating factors. Videos are particularly useful in teaching children. As schools are integrally involved in the daily life of the child, the family doctor should provide teachers with a record card which specifies treatment (regular drugs, prophylactics before games periods, and symptomatic relief for troublesome symptoms). Additionally children should carry with them a card which provides an action plan for emergency treatment at home and in the hospital.

### PHARMACOTHERAPY

The management section is divided into four age ranges. However, there are a number of common principles which span these groups. In each case there is a progression through a number of therapeutic regimes from the treatment of mild episodic asthma through to that of chronic, persistent and severe asthma. To a considerable extent, assessment of the severity of asthma is based on the response to treatment. However, mild asthma may be classified as discrete attacks occurring less than once a month, or as more frequent minor wheezes. All are responsive to bronchodilators taken no more frequently than two or three times a week. Moderate asthma can be recognised as discrete attacks occurring no more frequently than once a week, and in which no more than two to three doses (per week) of bronchodilators are required. In such circumstances, sodium cromoglycate prophylaxis would be indicated. More severe attacks tends to be less likely to respond to sodium cromoglycate. Attacks occur more than once a week and response to bronchodilators is sometimes poor. Inhaled corticosteroids are likely to be required in such circumstances with the addition of slow release $\beta_2$-stimulants and/or xanthines, particularly for nocturnal episodes.

In general, inhaled treatment at all stages is to be preferred. The dose of inhaled $\beta_2$-stimulants could be higher than that generally declared in drug data sheets. Thus if required in severe attacks, doses at least up to that which would be acceptable by the oral route could be inhaled—that is, 2 mg of salbutamol or 2·5 mg of terbutaline even for children as young as 2 years of age. The group felt that at present, apart from sodium cromoglycate, there was no effective alternative so called 'mast cell stabiliser', even though double blind trials of ketotifen have shown a small beneficial effect. The use of ketotifen, however, may be indicated in the treatment of atopic dermatitis and/or rhinitis associated with asthma. The dose of sodium cromoglycate initially should be administered four times daily, but may subsequently be reduced to two to three times daily if control is achieved. With powder inhalers, or nebulised solutions, 20 mg per dose is usually administered, and by metered dose inhalers 10 mg per dose is now preferred. However, 2 mg per dose may be used in countries where a 5 mg per dose actuator is not available. Inhaled corticosteroids must be administered using the minimal dose which adequately controls the disease. Beyond 600 μg/day of either beclomethasone or budesonide there is potential for detectable adrenal and growth suppression. However, it must be remembered that severe uncontrolled asthma can also have a significant suppressive effect on growth. Thus lack of an adequate therapeutic response indicates a need for more aggressive therapy. Lack of response may be defined as a requirement for $\beta_2$-stimulants more than two to three times per week.

If required in very severe disease, oral steroids should be given as alternate day treatment wherever possible. As there is not enough evidence that methotrexate or gold are appropriate treatments in childhood asthma, use cannot yet be recommended. There is no benefit in using mucolytics or antibiotics.

Attitudes to the value of xanthines in the management of childhood asthma have changed considerably in recent years. There is increasing concern about side effects which include irritability, insomnia, lack of concentration and poor school performance, headaches, nausea, vomiting, and abdominal pain. Such side effects can occur even when using doses in the acceptable therapeutic range. Interactions with viral infections, antibiotics, and many other drugs can sometimes push conventional doses into the toxic range which might lead to convulsions and even more severe consequences. Thus great care is required in using xanthines and in many parts of the world they have been relegated to very much a second line treatment, and then only in slow release formulations.

It is important to recognise when to reduce treatment. Because asthma is a chronic disease, however, patients should ideally be maintained free of symptoms for at least one year before instituting a trial of dosage reduction, which must be assessed using lung function measurements. A regular review of progress at all stages in the management of the disease is mandatory.

### IMMUNOTHERAPY

The role of immunotherapy remains controversial and the policy adopted in different countries varies. A subcommittee of the European Academy of Allergology and Clinical Immunology recently recommended that immunotherapy should rarely be used in children under 5 years. It should be used only when a clear unavoidable allergic trigger is identified. It is less effective when used in the more severe cases and may exacerbate uncontrolled asthma. As mild disease can be safely, effectively, and inexpensively treated with pharmacotherapy, the place for immunotherapy is restricted. It is most beneficial in patients with seasonal rhinoconjunctivitis with mild asthma. The United Kingdom Committee on Safety of Medicine has warned that immunotherapy must be under the direction and supervision of trained specialists for two hours after every subcutaneous injection.

Whereas treatment guidelines can be developed it is important to recognise the need for the individual patient to receive individual treatment. The ideal management is often achieved by a process of trial and error, utilising a rational sequence of therapeutic approaches.

### Management in the first year of life (fig 3)

In the first year of life treatment is often unnecessary in children with mild symptoms. However, those with more troublesome symptoms should be given oral $\beta_2$-stimulants and/or oral xanthines. In this age group $\beta_2$-stimulants are less likely to produce immediate benefit than in older children. If there is a failure to respond, the child should be referred for specialist assessment. The child can then be given inhaled $\beta_2$-stimulants from a metered dose inhaler using a spacer with a face mask system or a nebuliser. Nebulised respiratory solutions may produce a temporary deterioration in lung function which may be important if the baby is critically ill at the time. In this situation, nebulised solutions should be given in conjunction with oxygen, and the child should be observed in hospital to monitor any adverse reactions to treatment. Approximately 40% of wheezy babies in the first year of life show improvement in lung function with inhaled ipratropium bromide. Again, the nebulised ipratropium bromide could produce a temporary deterioration, lasting up to 10 minutes. This does not occur with aerosol administration from a metered dose inhaler and spacer.

Those babies with intermittent severe and persistent symptoms are more difficult to manage. Patients with persistent symptoms may be treated with sodium cromoglycate administered using a nebuliser. If the condition deteriorates further the use of inhaled steroids is indicated. A beclomethasone suspension is less effective largely because very little of the drug is in particles small enough to reach the lower airways, but a preparation of nebulised budesonide looks more encouraging. Inhaled corticosteroids can be given by a metered dose inhaler and spacer. If response to treatment is still poor and severe breathing difficulties are experienced, the addition of oral steroids, preferably on an alternate morning basis, may be necessary. Patients presenting with intermittent severe asthma can be treated using short courses of oral steroids.

### Management in the 1–3 year age group (fig 4)

In the second and third years of life, those with only occasional symptoms, associated with upper respiratory tract infections, can often be managed with $\beta_2$-stimulant syrups or oral xanthines. If the child is having intermittent but quite troublesome symptoms, or if side effects are intolerable on oral treatment he or she should be given inhaled $\beta_2$-stimulants, either using a nebuliser or metered dose inhaler with spacer. Those with troublesome symptoms that are not adequately controlled should receive specialist care. The appropriate treatment at this stage is nebulised sodium cromoglycate three times a day to which a $\beta_2$-stimulants can be added whenever the child has troublesome coughing or wheezing. Those children who fail to respond to the sodium cromoglycate can be tried on inhaled topical steroids, either as nebulised budesonide suspension or from a metered dose inhaler using a spacer with a face mask. Oral steroids (low, alternate day dosing) are advisable only when other treatments are ineffective.

Infrequent severe asthma symptoms can be controlled with inhaled $\beta_2$-stimulants administered using a nebuliser. If response to treatment is poor, short courses (three to seven days) of oral steroids and/or xanthines may be used in addition to the existing treatment.

### Management in the 3–5 year age group (fig 5)

Although some children in the 3–5 year age group with mild intermittent symptoms of asthma may only need oral $\beta_2$-stimulants, most will require inhaled $\beta_2$-stimulants. Most dry powder inhalers require the child to develop sufficient inspiratory flow rate at least 40 l/minute. Only older, wheeze free preschool children can generate this, and therefore powder inhalders should be reserved only for prophylactic treatment in these children. Once their condition deteriorates, however, their inspiratory flow rate is reduced and they derive less benefit from the powder treatment. In such cases the powder inhaler should be replaced with a metered dose inhaler with spacer or a nebuliser. In some, this treatment will be sufficient. $\beta_2$-stimulants may be used when the child is wheezy, as a prophylactic before exercise, or three times daily on a regular basis. If inhaled $\beta_2$-stimulants are required more than three to four times/week or symptoms are not controlled completely, continuous prophylactic treatment is required with nebulised, metered dose inhaler with spacer or dry powder sodium cromoglycate. Alternatively, slow release xanthines can be also used. Poor response is an indication for referral

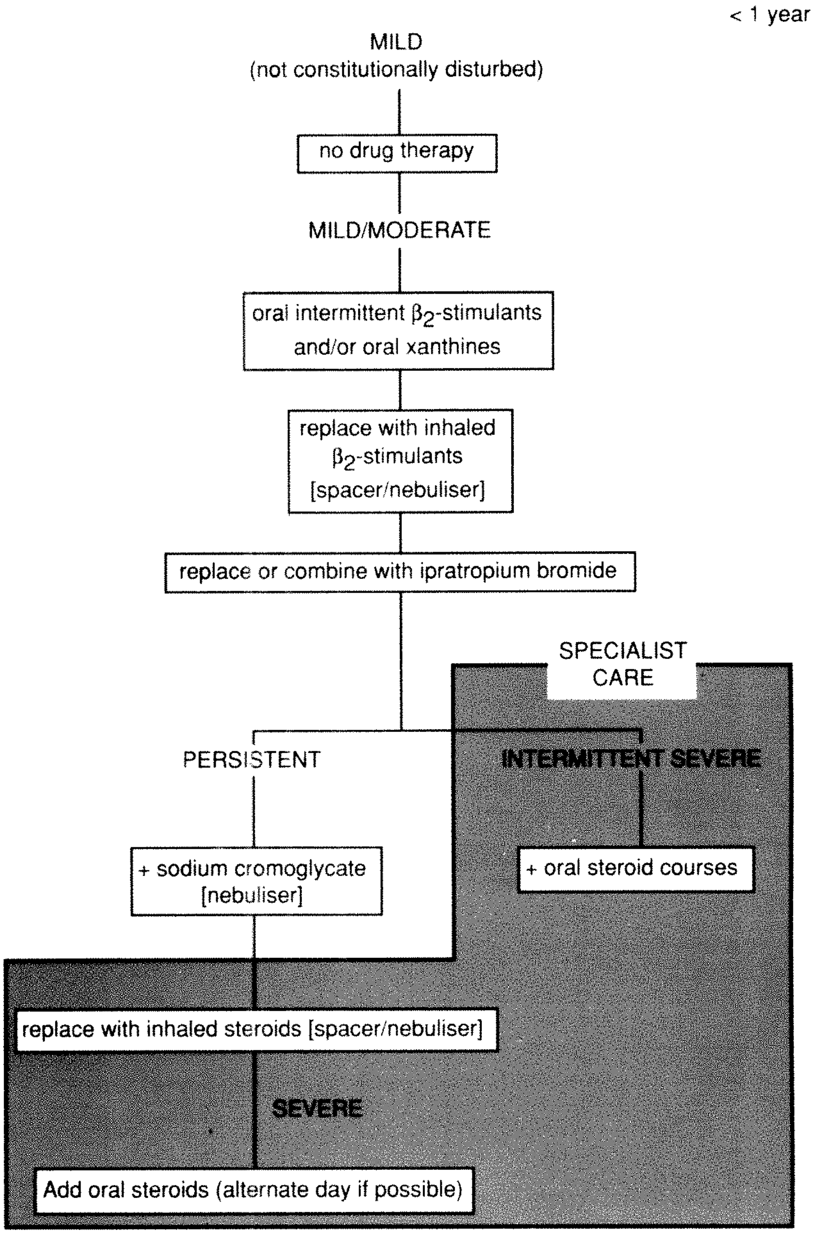
< 1 year
MILD
(not constitutionally disturbed)
no drug therapy
MILD/MODERATE
oral intermittent β2-stimulants and/or oral xanthines
replace with inhaled β2-stimulants [spacer/nebuliser]
replace or combine with ipratropium bromide
SPECIALIST CARE
PERSISTENT
INTERMITTENT SEVERE
+ sodium cromoglycate [nebuliser]
+ oral steroid courses
replace with inhaled steroids [spacer/nebuliser]
SEVERE
Add oral steroids (alternate day if possible)

Fig 3 *Management in the first year of life.*

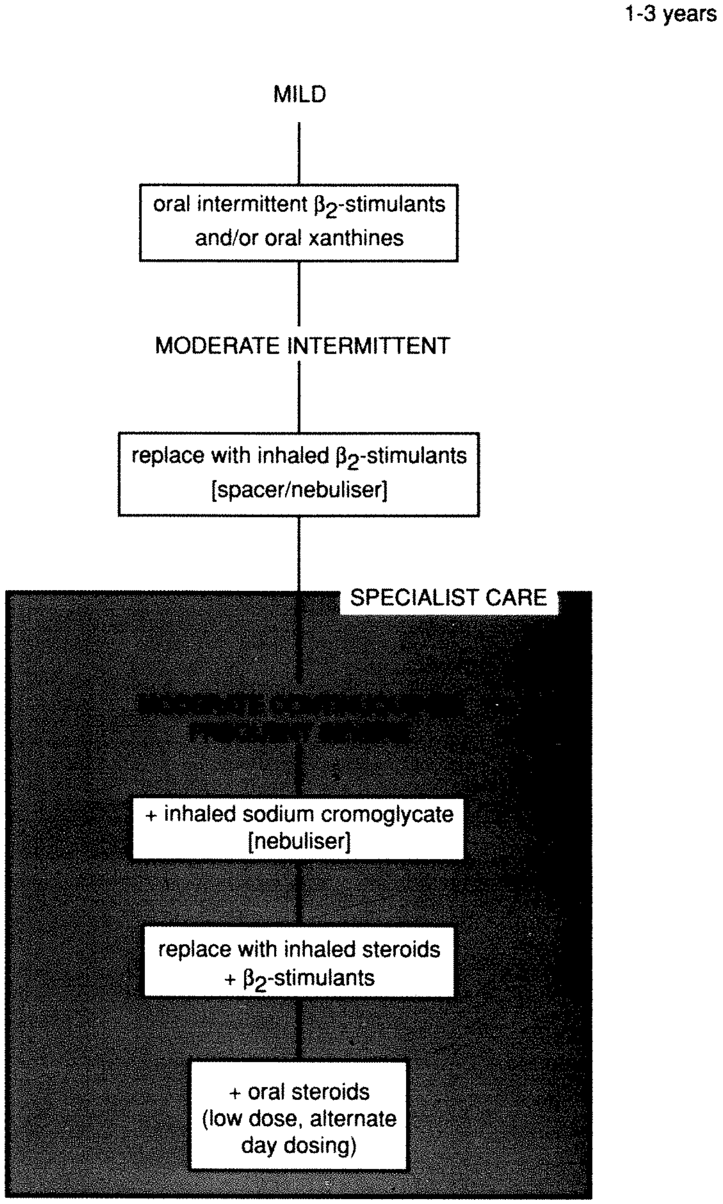
1-3 years
MILD
oral intermittent $\beta_2$-stimulants and/or oral xanthines
MODERATE INTERMITTENT
replace with inhaled $\beta_2$-stimulants [spacer/nebuliser]
SPECIALIST CARE
+ inhaled sodium cromoglycate [nebuliser]
replace with inhaled steroids + $\beta_2$-stimulants
+ oral steroids (low dose, alternate day dosing)

Fig 4 *Management in the 1–3 year age group.*

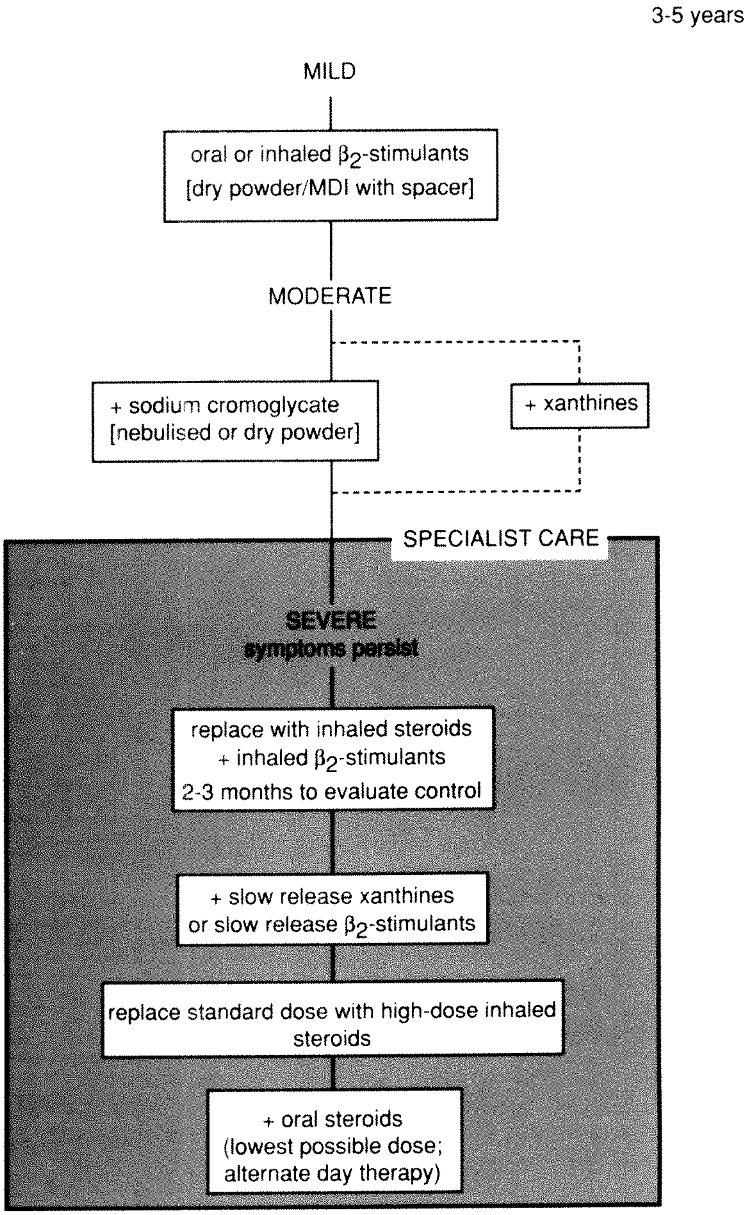
3-5 years
MILD
oral or inhaled $\beta_2$-stimulants [dry powder/MDI with spacer]
MODERATE
+ sodium cromoglycate [nebulised or dry powder]
+ xanthines
SPECIALIST CARE
SEVERE symptoms persist
replace with inhaled steroids + inhaled $\beta_2$-stimulants 2-3 months to evaluate control
+ slow release xanthines or slow release $\beta_2$-stimulants
replace standard dose with high-dose inhaled steroids
+ oral steroids (lowest possible dose; alternate day therapy)

Fig 5 *Management in the 3–5 year age group. MDI=metered dose inhaler.*

to a specialist. Inhaled steroids should be reserved for children with more severe symptoms or for cases where drug administration three to four times daily is not possible. Children, whose symptoms are not completely controlled by sodium cromoglycate and/or xanthines, may be given a six to eight week course of inhaled steroids to evaluate if they should be switched to this treatment instead.

Initiation of treatment with inhaled steroids is normally at a dose of 200–400 μg twice daily for the first one or two weeks. Thereafter, dose adjustments should be made on the basis of clinical response. Although no clinically important side effects have been reported, it is important always to use the lowest dose of inhaled steroid which controls symptoms satisfactorily. Often this can be achieved with a rather low dose once the child's condition is stable.

Slow release xanthines are given in doses sufficient to produce therapeutic blood concentrations (usually equivalent to 16–24 mg/kg/day of theophylline in two or three doses). When this treatment is prescribed it is important to be aware of possible side effects such as gastrointestinal symptoms, sleep disturbance, poor coordination, and impaired behaviour and learning. Oral $\beta_2$-stimulants in a twice daily, slow release formulation may be a suitable alternative.

Continuous treatment with oral steroids should be reserved for the very few cases who cannot be sufficiently controlled by other therapies. The lowest effective dose should be determined and used, and the possibility of alternate day treatment should be explored. However, this regime can normally be replaced by inhaled steroids.

## Management in the 5–18 year age group (fig 6)

Children over 5 years of age can use conventional inhaler devices if initial instruction is thorough. The introduction of dry powder inhalers and spacer devices has improved the success rate particularly in the early school age group (5–14 years).

$\beta_2$-stimulants form the first line of treatment for asthmatics in this age group. When used appropriately they can often ensure that the asthmatic child is able to lead an entirely normal life with only minimal symptoms. $\beta_2$-stimulants should be administered by inhalation so that the drug is delivered to the bronchial tree for more rapid action. By this route, smaller doses can be used, and adverse effects are minimised. The drugs can be inhaled either from a metered dose inhaler or from an oxygen or compressed air driven nebuliser. The efficiency of metered dose inhalers requires 'hand-lung' coordination, which can be improved by attaching a valved spacer device to the inhaler. Alternatively, a dry powder breath activated system can be used. Oral $\beta_2$-stimulants should rarely be used in this age group, although slow release preparations are occasionally considered for nocturnal symptoms.

Sodium cromoglycate should be used when symptoms occur more frequently. In young children, sodium cromoglycate may be given by inhalation as a dry powder. The usual starting dose is 20 mg, four times daily. When clinical response occurs, a maintenance dose of 20 mg, two or three times daily, may be adequate. A metered dose inhaler, delivering 1 mg per inhalation also has been shown to reduce asthmatic symptoms when given 2 mg, four times daily. In many countries a 5 mg metered dose inhaler is available and may be more effective in a dose of 10 mg three to four times a day. Long term use of sodium cromoglycate appears to be safe and virtually free from side effects. If troublesome coughing or wheezing are apparent, an inhaled $\beta_2$-stimulant should be added as required.

Inhaled steroids in the usually recommended doses are the next step of treatment in patients with frequent episodic asthma. Higher dose inhaled steroids can be used to improve overall control of asthma but at an increased risk of side effects, including adrenal and growth suppression.

For severe and persistent symptoms xanthines can be used, although they should be instituted in a stepwise regimen with regular monitoring of blood concentrations. In some countries xanthines would be utilised at an earlier stage. Physicians should also be aware of interactions between xanthines and other drugs. Ipratropium bromide may be added when maximum response with $\beta_2$-stimulants can not be achieved without side effects. In non-responders, oral steroids are necessary.

In the adolescent age group (14–18 years) there are several special problems: (1) some teenagers smoke but may not admit this to the family or doctor. The importance of smoking as a trigger factor should be highlighted and the habit aggressively discouraged. (2) Non-compliance and abuse of aerosols is a particular problem and cannister usage must be monitored closely. (3) Most childhood asthma deaths occur in adolescents. (4) Body image is important in adolescents and if asthmatic symptoms are not adequately controlled, the patient may suffer additionally from psychosocial problems. (5) Severe chronic asthma may stunt growth and delay puberty.

The first step in the non-pharmacological management of the adolescent asthmatic is counselling. It is essential to establish rapport. This can be a problem with adolescents and, if so, referral to a colleague may be helpful. Patients should be encouraged to

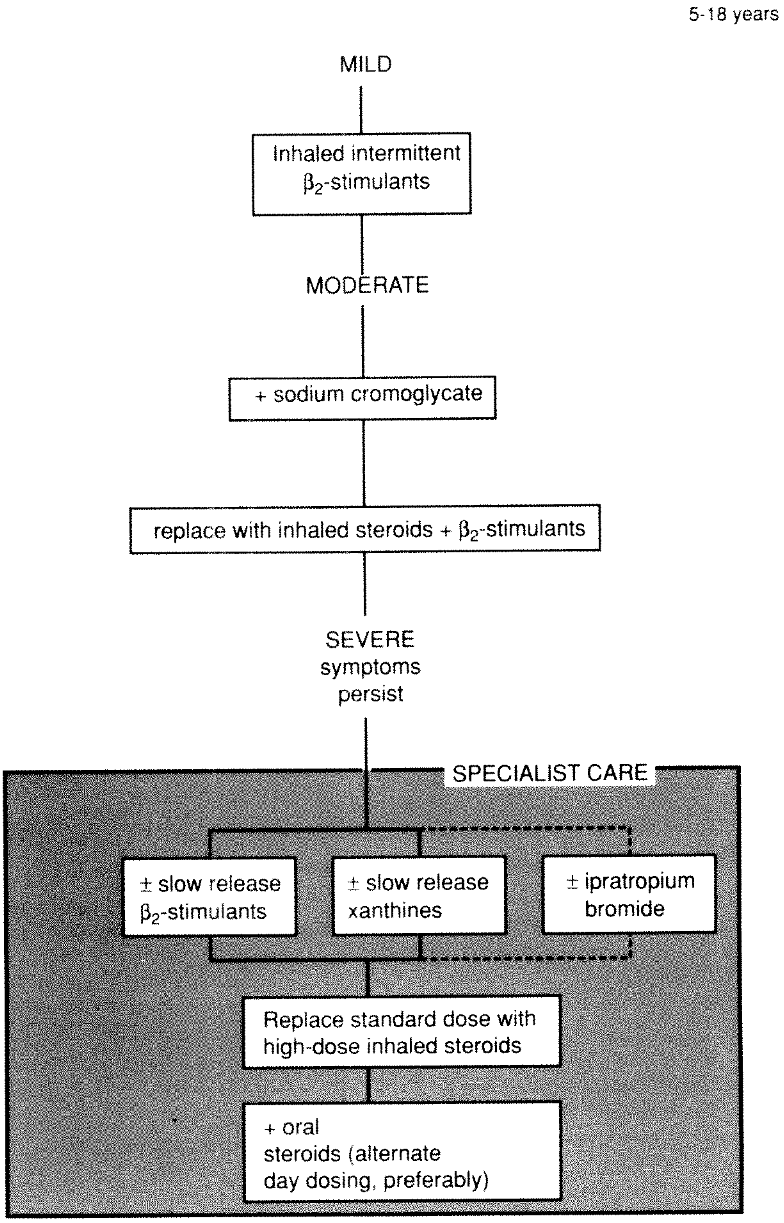
5-18 years
MILD
Inhaled intermittent $\beta_2$-stimulants
MODERATE
+ sodium cromoglycate
replace with inhaled steroids + $\beta_2$-stimulants
SEVERE symptoms persist
SPECIALIST CARE
± slow release $\beta_2$-stimulants
± slow release xanthines
± ipratropium bromide
Replace standard dose with high-dose inhaled steroids
+ oral steroids (alternate day dosing, preferably)

Fig 6 *Management in the 5–18 year age group.*

continue to participate in sport but should take prophylatic drugs where necessary and engage in preparatory warm up exercises. Even in adolescents, inhalers are often used incorrectly. Patients should be counselled to seek help when response to their emergency therapy is inadequate. It is important that adolescents do not feel different from their peers. Doctors should be prepared to see such patients out of school hours. Adolescent girls need to be monitored particularly carefully due to the greater likelihood of deterioration. Referral of adolescents to adult clinics should be planned with appropriate introductions and ongoing support. The development of adolescent clinics run jointly by paediatricians and adult chest physicians is to be encouraged.

When symptoms are not relieved by regular treatment, or peak flows are consistently reduced, teenagers should follow an emergency crisis plan. This is perhaps more appropriately referred to as an action plan in order to encourage use before a crisis develops. The action plan, which must be written, usually consists of increasing the doses of routine drugs, and, if necessary, adding oral steroids. A 'fast lane' facility with access to prearranged transport and admission to hospital may be required for those with a risk of severe attacks. Rarely, some will need access to subcutaneous $\beta_2$-stimulants or adrenaline and oxygen at home while awaiting transport.

## Management of acute severe asthma (fig 7)

Some patients, particularly in infancy, have infrequent severe attacks of asthma without any signs of asthma between episodes. When such cases have been identified it may be possible to outline and provide a schedule of treatment to handle such episodes at home. Nebuliser and air compressor units can be provided for inhaled $\beta_2$-stimulants given up to once every four hours with the addition of a short course of oral steroids (if using prednisolone 1–1·5 mg/kg daily in one or two doses) until the attack has subsided. Xanthine preparations may also be added to this schedule.

The need for emergency management of acute asthma attacks generally reflects under or delayed treatment which may arise from a failure by parents, patients, and doctors to recognise a deterioration in condition. Acute attacks should have been prevented by adequate prophylaxis and anticipation of problems during stress periods such as acute infection or seasonal high allergen exposure. At such times, an increase in prophylaxis may prevent acute attacks. Once an attack has failed to respond to the standard home treatment, however, medical attention will be required. General practitioners are advised to have an air compressor and nebuliser unit through which a maximal dose of $\beta_2$-stimulants can be administered at home. This will not only be therapeutic but will also provide an indication of the need for hospital referral. Failure to respond to the nebulised dose or relapse within four hours of a dose would indicate the need for referral. Response may be gauged on the basis of improvement in peak flow rate and a reduction in respiration rate with improved air entry in the lung fields. Cyanosis in air, the presence of pulsus paradoxus, or peak flow rates of less than 50% of predicted values after administration of bronchodilator would indicate the need for hospital referral. At this stage it would be appropriate for the general practitioner to give a loading dose of aminophylline by intravenous injection slowly over 20 minutes in a dose of 5 mg/kg. However, if the patient has been receiving an oral theophylline preparation it would be safer to avoid an intravenous theophylline preparation and to use intravenous salbutamol at a dosage of 10 microgram/kg given slowly. In addition either oral prednisolone 1–2 mg/kg or intravenous hydrocortisone 4 mg/kg could be administered.

On arrival at hospital, it is apparent that quite often inappropriate investigations and treatment are initiated. The key parameters to monitor are pulse, colour, the presence of pulsus paradoxus, peak flow rate, arterial blood gases, and/or oxygen saturation. Additional doses of nebulised $\beta_2$-stimulants should be administered. If the attack subsides, monitoring should be continued for at least four hours. If the patient remains stable during this period, they can be discharged home on continuing nebulised and oral treatment. If symptoms recur, or are unresponsive to this treatment, hospital admission is necessary.

After admission, the dosage and frequency of $\beta_2$-stimulants by nebuliser can be increased with the mandatory administration of oxygen. At the same time, oral prednisolone 1–2 mg/kg should be administered. Wheezing induced dehydration should be counteracted by appropriate hydration with the avoidance of over hydration which leads to pulmonary oedema. Under hydration could lead to drying of secretions and electrolyte imbalance which will compromise the effectiveness of treatment. This may necessitate the use of an intravenous infusion. Intravenous aminophylline in a loading dose followed by a continued infusion may also be added at this stage.

Once there is a failure of response to bronchodilators, the patient should be admitted to intensive care, continuing intravenous aminophylline and nebulised $\beta_2$-stimulants. Intravenous hydrocortisone 4 mg/kg every four hours should also be admin-

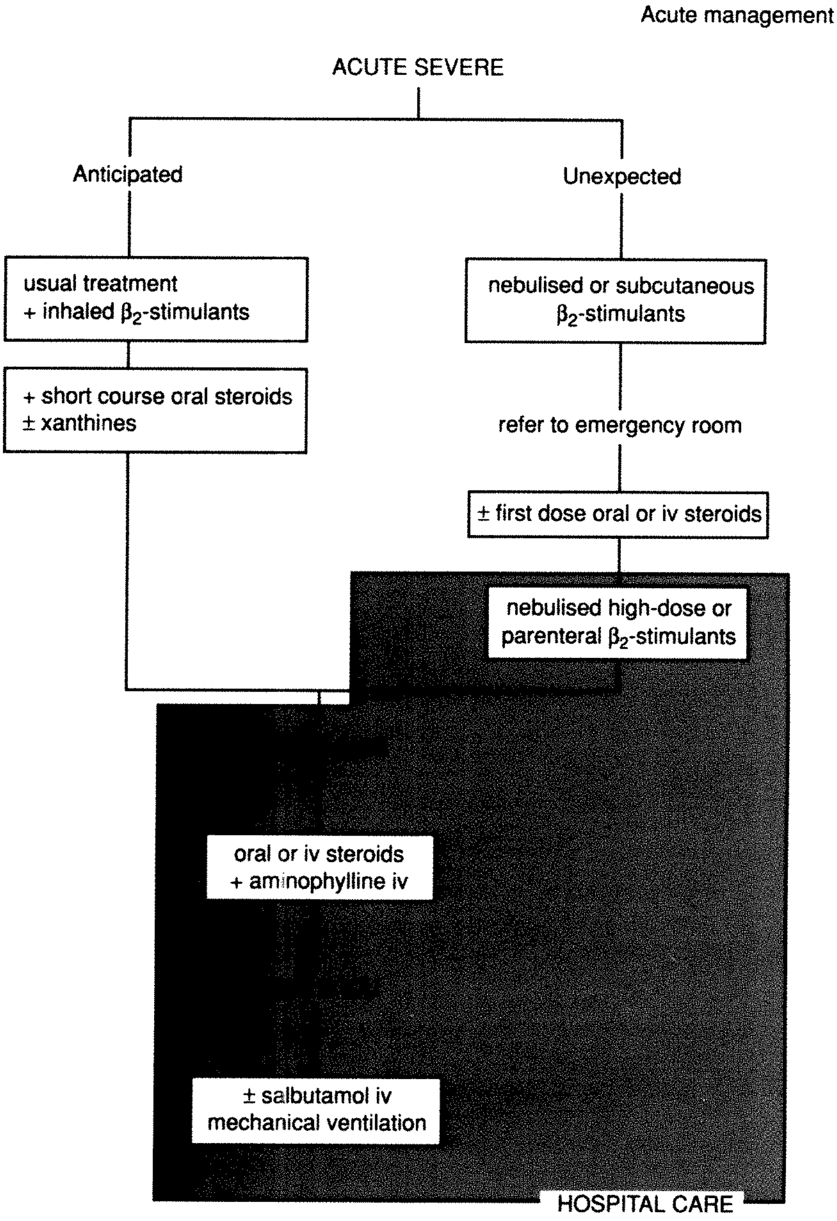

Fig 7 *Management of acute severe asthma. ICU=intensive care unit.*

istered. Blood gas monitoring will be required. Hypokalaemia may develop in response to treatment and requires correction. Downes criteria of carbon dioxide pressure >8·66 kPa (65 mm Hg) as an indication when to resort to paralysis/sedation and ventilation may lead to inappropriate and excessive numbers of patients being ventilated.

Finally an acute attack must always be considered a failure of prophylaxis and before discharge the regular treatment should be re-examined.

## Direction for future clinical research into management

During the course of the meeting, a number of areas were highlighted where there was clear need for further clinical research. Long term follow up studies of outcome in various situations are required. The frequency with which asthma is eventually manifested in individuals who are initially detected with asymptomatic bronchial hyper-reactivity is not known. Although there is an increasing demand for early introduction of aggressive asthma prophylaxis, the long term outcome of this approach, compared with symptomatic treatment, is unknown. Many individuals who have asthma throughout childhood become asymptomatic in adolescence or early adult life, but retain persistent defects of lung function with measurable lung overinflation. It is not known whether such patients should have continuing aggressive treatment and whether this affects the possibility of recurrence of the disease in later life. Similarly, it is uncertain whether an aggressive approach to the reduction of bronchial hyper-reactivity will improve the long term prognosis. During the discussion on therapy of asthma in the less than 1 year age group, it became apparent that there were very few controlled trials of any form of treatment. In particular, identification of the most appropriate and effective delivery systems for medication is required. The group accepted that immunotherapy had been established to be superior to placebo, but comparisons of this treatment with pharmacotherapy are necessary to evalute its role in the treatment of asthma. The efficacy of environmental manipulations, including the use of filters and ionisers, also requires further investigation. It was agreed that there is a need for new modalities of treatment in very severe oral steroid dependent asthmatics, and trials of the use of methotrexate, azothioprine, cyclosporin, oral gold and troleandomycin are awaited with interest.

This consensus statement was developed at a roundtable meeting (London, 3–4 December 1988) and was accepted by all the participants. Their contributions to the paper are gratefully acknowledged. *Steering committee*: John Warner, Consultant Paediatric Chest Physician, Brompton Hospital, London, UK; Tony Milner, Department of Child Health, Queens Medical School, Nottingham, UK; Mike Silverman, Paediatric Department, Hammersmith Hospital, London, UK; Manfred Götz, Consultant Paediatrician, Universität-Kinderklink, Wien, Austria; Søren Pedersen, Department of Paediatrics, Kolding Sygehus, Kolding, Denmark; Henry Levison, Chief, Chest Division, Hospital for Sick Children, Toronto, Canada; Louis I Landau, University Department of Paediatrics, Princess Margaret Hospital for Children, Perth, Australia. *Participants*: V Alzina, Spain; A Andreoli, Italy; A Backman, Finland; K Juntunen-Backman, Finland; KP Dawson, New Zealand; H von der Hardt, Federal Republic of Germany; D Hofmann, Federal Republic of Germany; JG Heurta-Lopez, Mexico; Y Iikura, Japan; N-IM Kjellman, Sweden; P König, USA; W Lenney, UK; HJ Neijens, The Netherlands; S Oseid, Norway; J Paupe, France; G Rachelefsky, USA; P Scheinmann, France; R Seger, Switzerland; JE Selcow, USA; MRH Taylor, Ireland.

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## *Personal practice*

# The electroretinogram

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SUMMARY The electroretinogram, findings, in response to a flash stimulus, was recorded from a skin electrode placed on the bridge of the nose in 4465 infants and children seen over a 10 year period. The electroretinogram was combined with a flash visual evoked potential. From this total, the electroretinographic findings in 240 patients, aged 1 day to 17 years, without suspected retinal pathology and with a normal visual evoked potential, were used as controls and normal electroretinographic parameters of different age groups defined.

There were 332 patients who showed an absent or very reduced amplitude electroretinogram. They were divided into primarily ocular disorders (n=195), neurodegenerative disorders (n=94), and various syndromes (n=43). Fundus examination did not always show any obvious abnormalities. The use of this simple and reliable technique for recording the electroretinogram made it possible to include this investigation as a routine procedure without the need for sedation in infants and uncooperative children. Electroretinographic studies, especially when combined with visual evoked potentials, and in some cases electroencephalography, may aid diagnosis in a wide variety of paediatric conditions, many of which have genetic implications.

Electroretinography measures the field potential of the retina in response to a flash of light and can be used clinically to assess retinal function (mainly rods and cones). The electroretinogram may show an abnormally small or absent response in retinal disorders even when in some instances there are no detectable abnormalities on ophthalmoscopic examination. In children there is a wide range of disorders in which the retina may be affected. Such disorders may be congenital or acquired and some evolve over a period of time. They include not only primarily ophthalmological disorders but also some systemic disorders or syndromes and certain neurodegenerative diseases.

In the uncooperative infant or child it is important to be able to record the electroretinogram reliably without the need for sedation or anaesthesia. Over the last 20 years a simple method using averaging techniques and recording from an electrode placed on the bridge of the nose has been developed in the department of clinical neurophysiology at the Hospital for Sick Children and some normal electroretinographic parameters have been published.[1] Recording of the electroretinogram has been combined with the cortical visual evoked potential and normal findings for the flash visual evoked potential at different ages have been reported.[2] The maturation of the electroretinogram, in response to a flash of light, and particularly from birth to 12 months, has not previously been described in any detail particularly with this technique.

In this study the normal electroretinographic parameters at different ages from birth to 17 years have been measured and all patients seen over a 10 year period showing a very reduced or absent response have been collected and grouped into diagnostic categories, in an attempt to give a comprehensive range of paediatric disorders in which an appreciable reduction or loss of the electroretinogram may occur.

## Patients and methods

Over a 10 year period, 1977–86, 5572 electroretinographic recordings (combined with visual evoked potentials) were made on 4465 patients referred to the department of clinical neurophysiology. Before this period, criteria of normality of the flash electroretinogram with the same technique was established in our laboratory in a series of 62 children aged 1–14 years with congenital heart disease. Although there have been only some changes in the averaging apparatus used since that time, it was considered worthwhile to measure the electroretinographic parameters in a larger number of children including infants less than 1 year and compare findings at different ages. For this purpose 240 infants and children from birth to 17 years of age were selected from patients seen in the last 10 year period. Although many of these patients had some neurological problems, mainly seizure disorders or retardation, or both, none had known ocular pathology and all had a normal flash visual evoked potential. These patients were usually more difficult to test than normal infants and children and therefore more comparable with patient groups investigated for ophthalmological problems.

From the total patients seen over this 10 year period, 332 were found to have an abnormal electroretinographic response, which was defined as absent or very reduced in amplitude (to less than half the expected size for age and conditions of testing). It should be noted that the number of patients with an abnormal electroretinogram was very much smaller than the number with an abnormal visual evoked potential.

Some details of techniques used in this department for recording the averaged skin electroretinogram (together with visual evoked potential) have previously been reported.[3 4] In brief, a silver disc electroencephalographic electrode was placed on the bridge of the nose and secured with sticky paper tape. Contact was made with electrode jelly and impedances of less than 2 Kohms obtained. An electrode placed over the vertex (using collodion) was used as a reference. A stroboscope (SLE) (emitting a flash set to produce 0·12 joules) was hand held close to the eyes (5·10 cm) and any head movements quickly followed. The room was not darkened during the procedure. Stimulation was at a rate of approximately 2/second except in infants under 12 months of age when slower rates were used. All children and infants were awake with the eyes open for as much of the time as possible. Great care was taken to exclude signals contaminated with movement artefacts or muscle action potentials and it was often necessary to interrupt and restart the collection of averaged data to achieve this. Ploys such as singing or tapping the glass of the lamp were used to keep the child still and quiet when necessary. Simultaneous bilateral eye stimulation was always carried out and, if a unilateral problem was suspected, monocular stimulation was achieved by holding a pad over the other eye. Many patients, especially young ones, had repeat studies to check maturation and progression of any disorder.

The electroretinogram was always recorded simultaneously with the flash visual evoked potential (derived from the mid occipital and right and left posterior temporal regions, also referred to the vertex). All signals were amplified using a Grass electroencephalograph machine with bandwidth of 0·3–100 Hz. Averaging was carried out using a PDP 11/40 general purpose computer with in house programs. At least 100 responses were averaged over a 250 ms epoch and repeated several times to ensure consistent findings. All patients had an electroencephalogram immediately before the electroretinogram and visual evoked potential investigations.

## Results

### NORMAL PARAMETERS

The averaged electoretinogram in response to a flash stimulus was recorded as a negative/positive complex ('a' and 'b' waves) of similar waveform though approximately one 10th the amplitude of that recorded with a corneal electrode using the same intensity stimulus.[1] The amplitude and duration of the components of the electroretinogram at different ages with the eyes open (bilateral stimula-

Table 1 *Normal parameters of electroretinogram at different ages*

| *Age (n=30)* | *Mean (2SD) amplitude 'a' (uV)* | *Mean (2SD) duration 'a' (ms)* | *Mean (2SD) amplitude 'a/b' (uV)* | *Mean (2SD) duration 'a/b' (ms)* |
|---|---|---|---|---|
| 0–4 Weeks | 4·0 (3·20) | 27·5 (7·64) | 8·0 (6·54) | 54·0 (17·58) |
| 5–12 Weeks | 6·0 (4·54) | 25·0 (7·94) | 12·5 (8·98) | 48·0 (14·72) |
| 3–5 Months | 8·7 (5·22) | 25·0 (7·26) | 17·0 (9·06) | 48·7 (18·60) |
| 6–11 Months | 10·0 (5·36) | 25·0 (5·46) | 21·7 (11·42) | 46·5 (11·86) |
| 12–23 Months | 11·4 (4·22) | 25·0 (6·30) | 25·0 (11·72) | 43·3 (7·90) |
| 2–4 Years | 13·0 (7·32) | 25·0 (4·74) | 25·0 (11·72) | 43·3 (7·90) |
| 5–10 Years | 13·5 (7·28) | 24·8 (4·80) | 31·7 (17·92) | 44·9 (13·6) |
| 11–17 Years | 13·3 (9·46) | 24·5 (4·80) | 29·3 (16·90) | 44·1 (11·70) |

tion) are listed in table 1. It can be seen that in the first month of life the electroretinogram is recordable with this technique, though the response is of very small amplitude and somewhat long duration. The amplitude progressively increases and the duration decreases and by 1–2 years of age are of relatively constant values (similar to those previously reported[1]). There is quite a wide individual variation in amplitude, however, especially in the older child as can be seen from the standard deviations given in table 1.

Representative electroretinographic records (bilateral stimulation) at different ages are shown in fig 1. The electroretinographic response from the same electrode with monocular stimulation is approximately half the size seen with bilateral

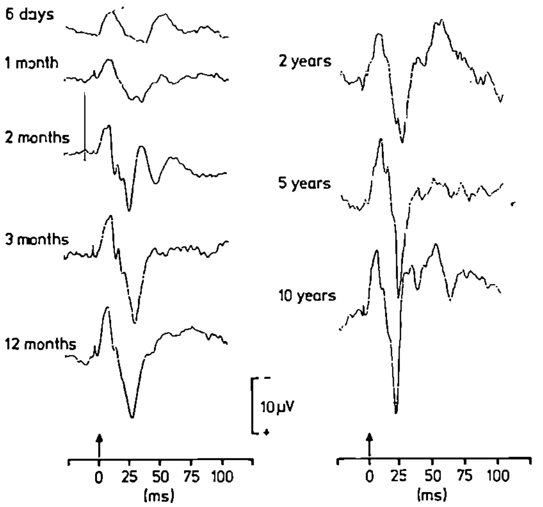

Fig 1 *Examples of normal electroretinographic findings at different ages with bilateral stimulation. Note the increase in amplitude of the 'a/b' complex, occurring over the first 50 ms after the flash stimulus (arrow), up to the age of 12 months.*

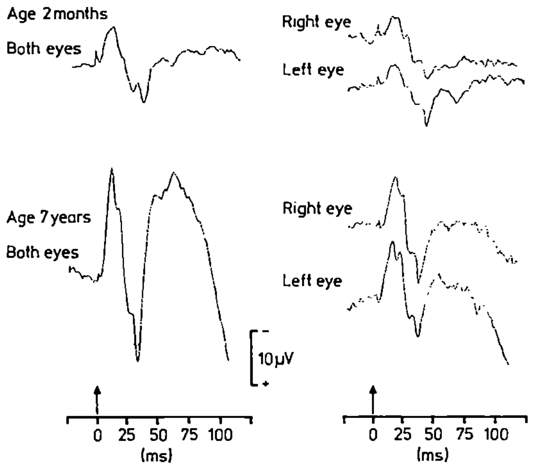

Fig 2 *Comparison of the electroretinogram with bilateral stimulation and monocular stimulation (covering one eye) in a young infant and child. Note the reduced amplitude of the 'a/b' complex with monocular stimulation but similarity between responses from each eye.*

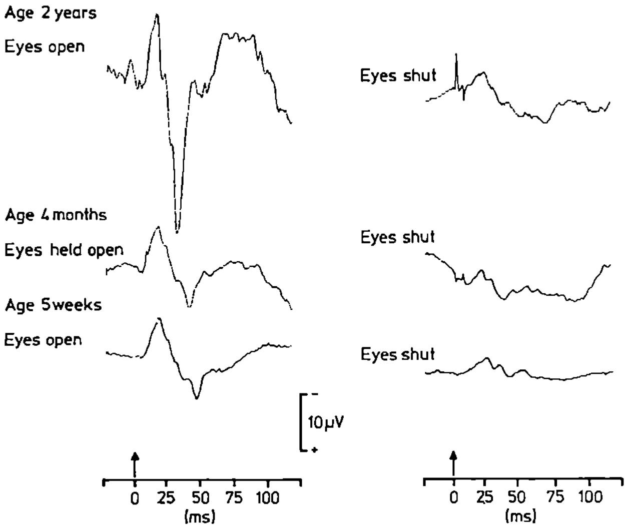

Fig 3 *Comparison of electroretinograms recorded with eyes open and eyes closed in three infants of different ages. There is an appreciable degradation of the response when the eyes are closed. In the sleeping state it is often possible to hold the eyes open and record the electroretinogram satisfactorily.*

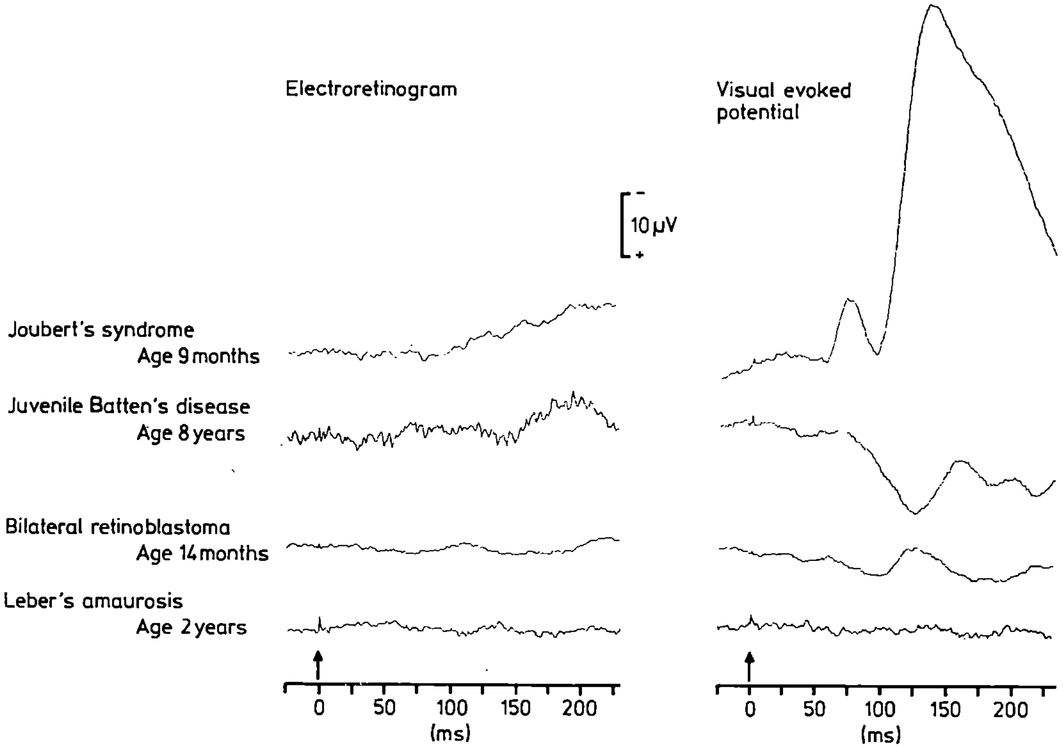

Fig 4 *Four children with an absent electroretinogram related to different conditions. Note the different visual evoked potential findings with a normal visual evoked potential seen in the infant with Joubert's syndrome and loss of main early negative component in the juvenile Batten's and retinoblastoma patients. The visual evoked potential is absent in the patient with Leber's amaurosis. The visual evoked potential findings may vary in all these conditions.*

stimulation (fig 2). If the eyes are shut a smaller and more prolonged response is recorded (fig 3) and ideally the response is recorded with the eyes open even if held open during the sleeping state (fig 3).

### ABNORMAL FINDINGS

The 332 cases in whom the electroretinographic response was absent or appreciably reduced in amplitude have been somewhat arbitrarily divided into primarily ocular disease (table 2), neurodegenerative disorders (table 3), and various syndromes (table 4). Some examples of combined electroretinograph and visual evoked potential findings in some of these disorders are shown in fig 4.

## Discussion

The technique for recording the flash electroretinogram as described has proved simple and reliable even in patients unable to cooperate. Some other workers have preferred to use skin electrodes placed under each eye that enables recording a separate electroretinogram from each eye. In our experience, however, these electrodes are not so well tolerated by the child who is young or retarded, or both, as a single electrode on the bridge of the nose. Although the electroretinogram thus recorded is the summed response from both eyes, abnormalities in most of the conditions described affect the retina of both eyes. A reduced amplitude electroretinographic response with bilateral stimulation will often suggest a monocular retinal disorder. If a unilateral retinal problem is suspected, it is more useful to cover one eye and not only record the monocular response but also the monocular cortical visual evoked potential. As the optic pathways from each eye pass to the visual cortex of both hemispheres, monocular stimulation is necessary if the integrity of the visual pathways from each eye to the brain is to be assessed.

Most patients with abnormalities on electroretinography show some fundus changes suggestive of a retinopathy and the fundal appearance of retinitis

Table 2 *Ocular disorders*

| | *No of patients* |
|---|---|
| Dystrophies: | |
| Leber's amaurosis | 60 |
| 'Retinal dystrophy' | 19 |
| Rod/cone dystrophy | 11 |
| Retinitis pigmentosa | 9 |
| Stargardt's disease | 1 |
| Gyrate atrophy | 1 |
| Choroideraemia | 1 |
| Malformations: | |
| Microphthalmos (with or without other) | 23 |
| Coloboma | 5 |
| Persistent hyperplastic primary vitreous | 3 |
| Retinal fold and hyaloid remnant | 1 |
| Retinal detachment | 11 |
| Retinopathy of prematurity | 21 |
| Retinitis/chorioretinitis: | |
| Congenital | 2 |
| Acquired | |
| Cytomegalovirus | 2 |
| Chickenpox | 1 |
| AIDS | 1 |
| Unknown | 1 |
| Retinoblastoma | 3 |
| Vascular: | |
| Retinal haemorrhage | 3 |
| Injury | 4 |
| Postsurgical | 3 |
| Osteopetrosis | 1 |
| Undiagnosed: | |
| With cataracts | 5 |
| Others | 3 |
| Total | 195 |

Table 3 *Neurodegenerative disorders*

| | *No of patients* |
|---|---|
| Batten's disease: | |
| Infantile | 1 |
| Late infantile | 16 |
| Juvenile | 32 |
| Variant forms | 8 |
| Mucopolysaccharidoses: | |
| Sanfilippo | 2 |
| Scheie | 1 |
| Hurler | 1 |
| Unknown | 1 |
| Mucolipidoses type IV | 2 |
| Hallervorden-Spatz disease | 1 |
| Mitochondrial cytopathy | 7 |
| Peroxisome disorders: | |
| Infantile Refsum | 2 |
| Zellweger syndrome | 2 |
| Spinocerebellar degenerations | 5 |
| Undiagnosed | 13 |
| Total | 94 |

Table 4 *Syndromes*

| | *No of patients* |
|---|---|
| Aicardi | 1 |
| CHARGE association | 1 |
| Cockayne | 1 |
| Ellis-van Creveld | 1 |
| Jeune | 1 |
| Joubert | 2 |
| Laurence-Moon-Biedl | 9 |
| Norrie's disease | 6 |
| Senior | 4 |
| Sjögren-Larssen | 1 |
| Usher | 3 |
| Walker-Warburg (HARD±E) | 2 |
| Undiagnosed | 11 |
| Total | 43 |

pigmentosa is well known. This is not always the case, however, most notably in the young patient with Leber's amaurosis.[5] Conversely some retinopathies—for example, rubella—do not show abnormalities on electroretinography and visual function is not always compromised.[6] In patients who are difficult to examine clinically, the presence of a normal electroretinogram is some reassurance that there is no appreciable loss of function of outer retinal layers. In the presence of cataract, fundus examination may be limited. In our experience the flash electroretinogram is normal in most patients with cataracts unless retinal pathology is present and an abnormally reduced or absent electroretinographic response in the presence of cataract is indicative of retinal pathology. The few cases of cataracts with abnormal findings listed in table 2 are presumed to have other unidentified ocular disease. Nystagmus was a very common symptom in many patients, with or without retinal pathology, and has not been considered as a separate entity.

The flash electroretinogram is mainly derived from peripheral photoreceptors and its absence does not necessarily imply that all retinal function has been lost. As the flash visual evoked potential is a mainly macular response, the combined recording of an electroretinogram and visual evoked potential may be helpful in distinguishing between peripheral and macular retinal problems. Thus an absent electroretinographic response can be associated with a normal visual evoked potential in patients with some preservation of macular function (fig 4) and is usually associated with reasonable vision.

The commonest diagnosis in the primary ocular group was a retinal dystrophy. The diagnosis of unclassified retinal dystrophy can only be made by exclusion of other known causes for reduced vision and retinopathy by biochemical screening (amino acids, phytanic acid, urine osmolality, creatinine clearance, mucopolysaccharides, blood lipids). The cone/rod dystrophies are considered as a distinct subgroup. In this study the electroretinogram has been recorded under photopic conditions and, although, even with a non-corneal electrode, rod and cone responses can be distinguished using flicker fusion or varying spectral frequencies of stimulation, this has not been routinely carried out.

The most commonly diagnosed retinal dystrophy was Leber's amaurosis, first described by Leber in 1869,[7] in infants who before the age of 1 year show appreciably reduced vision, nystagmus, and poor pupillary reactions. It is regarded as having an autosomal recessive mode of inheritance. In 1954 Franceschetti and Dieterlé added an absent or appreciably reduced electroretinographic response to the diagnostic criteria.[8] The fundus appearance varies from normal to a retinal dystrophy like picture. The disease can have systemic associations such as renal and neurological disease.[9] Because of the varied presenting clinical signs and differing fundus appearances, the electroretinographic findings have been considered crucial in making the correct diagnosis.[10]

As the electroretinogram shows a mass retinal response to light stimulation, it is obvious that any condition that destroys a large amount of retina such as gyrate atrophy and choroideraemia as well as a large retinoblastoma will affect the response. In coloboma of the eye there is thought to be defective closure of the fetal fissure, leaving a defect which in the retina is replaced by glial and fibrous tissue. Depending on the size of the coloboma and therefore the amount of retina affected, the electroretinogram may or may not be reduced. Bilateral macular dysplasia ('colobomata') has been described in association with retinal dystrophy,[11] with the retinal responses disproportionately small to the size of the coloboma.

In the more severe forms of retinopathy of prematurity in which there is an abnormal vascularisation of the retina, the retina becomes detached and the electroretinographic response is appreciably reduced. The retina may also became detached in persistent hyperplastic primary vitreous and so reduce the electroretinogram. In severe microphthalmia the retina is poorly developed, especially as it is frequently associated with a coloboma, explaining both the poor vision and the reduced electroretinogram. In primarily macular disorders such as Stargardt's disease, enough peripheral retina may be affected to reduce the response. Surgical procedures including resection of an optic nerve glioma may compromise the ocular circulation and thus account for electroretinographic abnormalities in such cases. Hoyt and Billson first described a small or absent electroretinogram in three patients with the infantile form of osteopetrosis (an abnormal response has only been found in one of six patients we have examined), despite a normal fundus appearance.[12] They suggested that visual loss in these patients may be the result of retinal degeneration rather than solely due to optic atrophy, although the reason for any retinal pathology is not clear.

In our series by far the largest group of neurodegenerative disorders showing electroretinographic abnormalities were the various types of Batten's disease (neuronal ceroid lipofuscinosis). Diagnosis can be confirmed by histological examination only (as no biochemical defect has been identified) and combined clinical neurophysiological assessment has proved of considerable value in suggesting the diagnosis.[13] In all types of Batten's disease the electroretinogram is affected at a relatively early stage, particularly in the juvenile form which usually presents at 5 to 6 years of age with visual problems. It should be noted that the flash electroretinogram is not affected in the various types of gangliosidoses as only the ganglion cell layer of the retina is involved in these disorders.[14] While the electroretinographic findings may not be important in the diagnosis of the mucopolysaccharidoses, it may often be worthwhile carrying out electroretinographic studies to monitor any progression of retinal dysfunction especially in the presence of cataracts. Reduction of the electroretinographic response, however, may be helpful in the diagnosis of rarer disorders such as mucolipidosis type IV[15] and Hallervorden-Spatz disease, and in our experience progressive changes may occur over a number of years in both these diseases. In the newly recognised peroxisome disorders[16] it seems that electroretinographic abnormalities may be present from an early age,[17] as we have found in infantile Refsum's disease and some cases of Zellweger's syndrome. An absent electroretinogram has been reported in infantile adrenoleucodystrophy,[18] although as yet we have not seen any cases with this diagnosis.

The diagnosis of a syndrome is based on the recognition of a pattern of associated anomalies. In some of the syndromes listed in table 4 there is an associated pigmentary retinopathy as for example, Laurence-Moon-Biedl, Senior's[19] and Joubert's[20] syndromes. There are also causes for a reduced response other than in a retinopathy as for example, coloboma in CHARGE syndrome,[21] chorioretinal lacunae in Aicardi's syndrome,[22] retinal malformations in Norrie's disease,[23] and retinal dysplasia in Walker-Warburg's syndrome.[24]

In the progressive neurological disorders and in many of the syndromes listed, the electroretinogram is progressively reduced in amplitude over the course of months or years, usually paralleling changes in vision (and also in visual evoked potentials). In conditions such as eye injury (including non-accidental injuries) and retinal haemorrhages (secondary to for example, hypertension or leukaemia), the extent of retinal abnormality is variable and determines whether or not the electroretinogram is affected. This is also the case in infections whether congenital, such as toxoplasmosis or cytomegalovirus, or acquired (seen mainly in immunosuppressed patients in our series). It should also be noted that in most of the syndromes described, retinal involvement (and consequent electroretinographic abnormality) is not invariable. In a disorder such as mitochondrial cytopathy, which has such a very variable clinical expression, it is not surprising that less than half the cases we have seen show electroretinographic abnormalities.[25] Associated deafness may occur in mitochondrial cytopathy and in some other conditions as for example, Usher's and Senior's syndromes and infantile Refsum's disease among others.[26] The auditory problem can be documented using brain stem auditory evoked potentials in the very young or uncooperative child, and the combination of abnormalities found on electroretinography and brain stem auditory evoked potentials may be important in delineating some of these disorders. In addition the presence and type of any electroencephalographic abnormalities may also be important in suggesting the nature of any associated cerebral involvement in some of the conditions described especially in some of the neurodegenerative disorders.

Recording of the flash electroretinogram appears to have been a somewhat neglected investigation, especially in children, perhaps because it has generally been believed that it is only possible to carry out using corneal electrodes under general anaesthesia. As outlined in this study, however, reliable recordings can be obtained as a routine procedure in the waking state, without any need for cooperation, and avoiding anaesthetic risks. Most departments of clinical neurophysiology now have averaging equipment available and recording the electroretinogram from skin electrodes is quite feasible using averaging techniques. There are advantages in electroretinography being carried out in clinical neurophysiology units where evoked potential studies and electroencephalography can also be carried out as appropriate. The integrated reults often give much more information than any one test alone, especially in disorders that may involve the brain or auditory pathways, or both.

It is appreciated that the disorders discussed in this survey do not comprise an exhaustive list of all paediatric conditions in which the electroretinogram may be affected. Furthermore over the 10 year period of this survey the diagnostic categories have widened and some patients seen in the earlier years and, in particular, patients diagnosed as Leber's amaurosis would now be given a different diagnostic label as awareness of conditions such as Joubert's syndrome, cone dystrophies, and congenital stationary night blindness have been appreciated. While it is not claimed that the flash electroretinogram recorded with this technique can detect subtle or early retinal involvement, the results show that the finding of a reduced or absent response is often essential in the diagnosis of a wide variety of not only ocular problems but also some neurodegenerative conditions and is a pointer towards the identification of some syndromes. As there are genetic implications in a number of these disorders, the importance of a correct and early diagnosis cannot be over emphasised.

We are grateful to the physicians and surgeons for referring patients for these studies, in particular the neurologists Dr J Wilson and Dr E Brett. It is a pleasure to acknowledge the help of the technicians whose patience and skills made these recordings possible.

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***Personal paper***

# The school health service through parents' eyes

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## Starting points

The school health service, like most services with a long history, has changed its shape considerably since its inception. Started in the wake of concern that so many potential recruits to the armed forces were medically unfit for the Boer War, its broad based inspections of children began in a context where medical care was by no means free at the point of access, and where living conditions for the majority fostered ill health and the spread of disease. While we still have children whose health is affected by poverty and poor housing, the profile of childhood and adolescent ill health has changed, and the school health service has therefore changed with it.

There are those who argue that it has not changed enough, and that its objectives require more precise definition so that resources may be used more effectively. This, of course, could be said of much of the work of the caring professions. It is also argued that services should make their aims and methods clearer to the consumers, be they patients or clients, giving them full explanations and a sense of individual involvement in their own care. These two motives prompted a short research and development project in Nottingham based around parents' perceptions of the school health service. The district community unit was engaged in a general process of reviewing service provision in relation to service objectives; Trent Regional Health Authority was promoting pilot schemes for 'personalising the service' and wanted a community example. It was thought that a knowledge of parents' views of the service would help professionals sharpen up their own objectives in the process of working out how to tell parents what they needed to know.

The purposes of the school health service are not easy to define briefly. It has a dual role. On a routine basis, it provides a continuation of the regular surveillance and immunisation offered to all children through the child health clinics, aiming to identify problems before they become serious, or to confirm that all is well. School doctors and school nurses develop expertise in educational medicine so that they can advise parents, teachers, and children when health and educational problems intertwine, as is often the case. They can thus offer a specialist service for some children in addition to the general preventive care available to all. Increasingly the general preventive care is provided through a system of appraisals by nurses with selective medical examinations arranged on the basis of previous findings or referrals. Many referrals come from the nurse; in theory, however, parents and teachers also have parts to play in identifying children who seem to have problems, and in referring them for help.[1] Do parents and teachers understand the system and their role within it well enough to use it successfully? It seemed unlikely. The limited work that has been done on teachers' knowledge[2–4] suggests that there are, indeed, large areas of ignorance; parents are likely to know even less. In Nottingham an attempt was made to find out what parents know, what they would like to know, and how they would like to be informed, as a preliminary to improving the situation.

## Method

In all, 119 parents were interviewed in 17 different locations, varying in the extent and organisation of medical staffing, and including middle class and 'deprived' areas. To maximise contact with parents within the constraints of funding, schools and day nurseries known to have good relationships with parents were approached for help. Mother and toddler groups, parents's groups, school clinic, and school medical waiting rooms were used to conduct informal semistructured interviews with individual parents or small groups. The sample was thus not random; it was deliberately biased towards primary school parents where contacts with schools are closer, and towards institutions interested in making services more accessible to parents. This could be seen as a methodological flaw, introducing a bias towards knowledgeable parents. The interview schedule mixed open questions about what parents would like to know and how they would like to be informed, with a series of specific probes. These concerned parents' knowledge of the school nurse, the school doctor, the standard information sheet issued to all parents when a child started school, and the school clinic. The nature of the settings used—often semipublic—might have made parents less inclined to admit ignorance; again, the results of this enquiry are therefore likely to overestimate parental knowledge.

### General knowledge of the system

Despite the bias in the sample the raw results of the survey show widespread ignorance about the nature, purposes, and workings of the school health service (table). Quantifying the results of the question on school clinics had to be abandoned because confusion was so widespread about the nature, function, and whereabouts of the clinics, in part the result of the varied approaches taken to clinic staffing and their possible 'drop in' function.

The results indicate in figures what the interviews confirmed in more general terms. The comparatively high figure for parents knowing that there was a school nurse attached to their child's school (67%) should not induce complacency; there is not much purpose served by parents knowing there is a nurse unless they also know who she is, how to contact her, and that contacting the nurse with specific kinds of problems is an acceptable use of the service. This information was generally lacking. As might be expected, the figures for doctors are much worse; not all schools in the sample had doctors attached, but where they existed their impact on parents seems to have been in general limited. The few examples of parents who knew the name of the school doctor were almost all found in a clinic where the doctor had his name on the door, a practice not seen elsewhere.

### Parents learning

These figures suggest that the 'official' sources for parents to learn about how the school health service works were ineffective. The interviews showed how parents had to rely on a number of unsatisfactory sources of information for what little knowledge they had. They learnt mainly from children's reports ('A lady came to school and combed our hair'), their own experience (remembered as thorough and regular, if incomprehensible), and the 'bush telegraph', which brought rumours of clinics with helpful doctors. These sources are hardly an adequate basis on which to build an understanding of the workings of a complex system, one which head teachers frequently admitted baffled them too.

It is not surprising that the researcher received frequent requests for information about what the service was for, how it worked, and what could be expected. When the school health service was explained as an extension of the baby clinic some parents were enthusiastic, wanting to know precisely what was being investigated so that they could get involved as well. There was also criticism. Parents wanted to know when the nurse was coming, so that they could raise problems and also so that they could ease her work ('If I'd known I wouldn't have plaited her hair'). As they had never been told about the principles of selective medicals, some parents not unnaturally thought there were too few examinations. As they had little idea of the expertise of the specialist staff or of what they might be looking for, some parents understandably compared the school health service with that offered by their own family doctor. Some who felt that they had a helpful general practitioner who was 'good with children' said that if there was anything wrong they would naturally go to him. Others were scathing about their general practitioner and correspondingly appreciative of the helpfulness of the nurse and doctor they saw through the school. The widespread ignorance and confusion about the service made it impossible to define the size of each group; this would require a separate study requiring planned educational input to see that parents knew what the service was about before they were asked what they thought of it.

### Parents' impressions: do they matter?

The impression of the service gained from parents in this study was one of confusion and randomness rather than of the planned systematic approach to child surveillance that the service is attempting to apply. The general parental bafflement was relieved only by current helpful experience with a particular child or by a personal relationship with a member of

Table *Parents' knowledge of specific issues*

| | % |
|---|---|
| Remembered information sheet | 4 |
| Knew that there was a nurse attached to school | 67 |
| Knew the name of the school nurse | 21 |
| Knew that there was a doctor attached to school | 26 |
| Knew name of school doctor | 11 |

the school health service—usually, but not always, the school nurse. The bafflement was usually inarticulate: in deprived areas it was often accepted as inevitable, and in middle class areas it was often confessed with embarrassment as if it was a failure in parental duty. It seems appropriate, however, to quote two parents from different areas whose comments were trenchant and telling. Both women were articulate, competent and unembarrassed; there was no sign of guilt about their lack of adequate information.

*A middle class mother in her thirties:*

'I didn't know there was a school health service as such—it seems to be just bits and pieces. My level of ignorance about people and services is so great that it is difficult to know whether it would help to know the names of the nurse and doctor'.

*An inner city mother in her twenties, ex-nursery nurse:*

'It's no good telling people [in a leaflet] how the system should work, because it doesn't. Tell people that if they have a problem, this is what *may* be available, and give them a contact point of someone to talk to, or who would ring them back'.

If parents have no problems, it seems poor public relations, at least, to let them retain a view of the school health service as random, confused, recently abolished (a middle class view), or lacking a cohesive identity. If parents do have problems, such a view presents an obstacle to seeking help (for what help could such an organisation give?) or to using its resources to the best advantage to help their child, once contact has been made. Parents' responsibilities cannot reasonably be expected to be carried out in the absence of clear information on the kind of diagnostic and support services available, and on what parents are expected to do themselves.

How much do names matter? It has been suggested that they matter because they are an efficient way of contacting people again. The case for knowing the identity of staff responsible for the care of your child goes beyond efficient contact, however. There are primitive tribes who take great care to whom they give their names, for to tell someone your name gives them power over you. It is not necessary to believe in magical consequences to recognise that there is a power imbalance between the professional on the one hand, who is in possession of the child's notes which may include considerable detail on the family, and the parents on the other, who are faced with a doctor or nurse who effectively withholds even a name. If the school health service is intended to work in partnership with the parents for the welfare of the child, a little more equality would seem to be indicated.[5–7]

## Practical implications

Parents were asked how they would like to be informed. Most said that a leaflet would be helpful; some stressed the virtues of clear simple English and attractive presentation, features somewhat lacking in the old information sheet about which head teachers had been either constructively critical or scathing. Parents also wanted to know the name, telephone number, and base of their school nurse and school doctor. They wanted a clearer idea of what the school health service offered, and advance notice of nursing as well as medical visits to see their children. They wanted to be told of the results of examinations, even if they could not attend medicals because of other commitments. Reassurance that all was well was valued.

All of these seemed reasonable. Some were easier to act on than others. The project was extended to cover the development of materials—leaflets for parents with a space on the back for the name and address of the school nurse, doctor, and clinic; posters to advertise the school nurse, and name badges and labels for desks and doors; and a booklet for teachers to explain the system to them, as they also needed to know more.

All these measures are comparatively cheap. In the current climate of increasing financial stringency in the health service they may be good investments. The public will protest at cuts in curative services for children when the headlines scream about babies dying because of the lack of the latest technological equipment; it will even subscribe to the appeal to 'Save Great Ormond Street'. How many parents would protest about cuts in a service they do not understand and which fails to communicate in such elementary ways? Doctors working with children know that they need to work with parents too. In the school health service, there need to be ways in which parents can see what is on offer and how to use it properly. The sooner these are developed, the better for all concerned.

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# Referees 1987–88

During 1988 there was a change in our recording system and this has resulted in the omission of the names of some of our referees from the list published last December. We thank the following for all their hard work for the journal and apologise to them and others we may have failed to trace.

Adlard P
Allan L
Ansell B
Atwell J
Bacon C
Bailey C
Bartlett K
Bax M
Beardsmore C
Beattie T
Bower B
Brueton M
Burr M
Challacombe D
Cockburn F
Colley J
Cutting W
Dodd K
Dunger D
Dunn P
Eady R
Evans J
Garralda E
Goodall J
Goodchild M
Hall D
Halliday H
Harper E
Harper P
Haworth S
Herber S
Hodgson J
Holt L
Horsman A
Insley J
Jones B
Keen J
Kiely E
Kilby A
King J
Kirkham F
Kroll J
Lambert P
Levin M
Marcovitch M
McCarthy G
Meadows N
Mehta A
Mehta V
Mellor D
Newman C
Postlethwaite R
Pullan C
Raine P
Rennie J
Rigby M
Ross E
Schwartz R
Speidel B
Steer P
Stevens M
Stevens R
Swift P
Tam P
Taylor B
Thomas D
Verity C
Wales J
Waterston A
Whale K
Whitmore K
Wright J

*Archives of Disease in Childhood,* 1989, **64,** 1092–1097

# Correspondence

## Intervention after birth asphyxia

Sir,

In his article on this subject Dr Whitelaw rightly stresses the reality that 300–400 children per year are surviving birth asphyxia with serious brain damage.[1] He also mentions that withdrawal of intensive care in the worst cases is viewed as both ethical and humane by many paediatricians. He then questions whether we are being too negative.

His final sentence fills me with alarm. He suggests trials of newer treatments in those infants with the worst prognosis. While this may be most satisfactory for the scientist, I would suggest it is least satisfactory for the humanitarian as it is precisely these infants who would be eligible for a policy of withdrawal of intensive care. If a trial is undertaken and infants receive maximal support for the duration of the trial, there is a high risk that a negative therapeutic result will result in an increased survival of severely brain damaged infants. This appears to have already happened in Eyre's work on thiopentone induced coma to which Dr Whitelaw refers. This is an area where scientific and therapeutic enthusiasm can be a vice not a virtue.

Surely Dr Whitelaw's recommendations should be reversed and newer treatments should only be used on those mild and moderately affected infants who seem destined to survive. This will have the disadvantage that differences will be harder to prove, but will have the advantage of being perfectly justifiable on ethical grounds.

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Dr Whitelaw comments:

I am grateful for Dr Speight's thoughtful contribution. I cannot agree with his view that trials of new treatments in birth asphyxia should be restricted to mild and moderate cases. Such infants have, with current treatment, a good outcome in nearly all cases. To use new agents such as calcium channel blockers or glutamate antagonists in infants with a good prognosis is not justified as there is a real risk of the treatment itself having adverse effects. Research conferences have already heard anecdotal reports of circulatory depression with calcium channel blockers.

To use a new treatment with the possibility of adverse but manageable effects is surely more justifiable in desperate clinical situations where current therapy usually fails. Thus I favour trials of new treatments being limited to infants who have a bad prognosis by objective criteria.

Let us examine Dr Speight's suggestion that one possible outcome of such a trial of new agents could be increased survival of severely brain damaged infants. It would be essential for parents of infants eligible for such a trial to be fully informed about the range of likely outcomes and the available options. Parents would be free to refuse entry to the trial and free to withdraw at any time. Just as parents (or staff) are free to discuss withdrawal or support now, so would they be in a trial.

The experimental evidence suggests that the 'therapeutic window' during which intervention is likely to protect the brain, is probably less than 48 hours and therefore prolonged intensive care support need not be part of the trial protocol. Thus a decision to stop treatment could be made after a few days if parents and staff were unanimous on the failure to show any improvement.

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[1] Whitelaw A. Intervention after birth asphyxia. *Arch Dis Child* 1989;**64:**66–80.

## Intraspinal tumours

Sir,

This leader usefully stresses the subtle, often insidious presenting features of intraspinal tumours.[1] However, there are a number of important omissions and errors of fact, as follows:

(1) Space occupying lesions below L1–2 (L2–3 in infants) cause cauda equina compression, not spinal cord compression. The distinction is important because the risk of myelography, and of lasting neurological handicap, is less in the case of cauda equina compression. In making management decisions, there is a lesser degree of urgency.

(2) In the case of neuroblastoma the lesion causing cord/cauda equina compression is most commonly the *primary* tumour but, in 20–40% of cases a secondary (metastasis) is responsible.[2] This distinction is critical because the treatment strategy (see below–No 6) may be quite different in these two sets of circumstances.

(3) There is no 'predeliction' for neuroblastoma to present in the newborn period: in fact, the peak (median) age incidence is in the third year of life.[3] It is, however, true to say that neuroblastoma is the commonest malignant tumour occurring in the neonatal period.

(4) Dr Cole's claim that '. . . refinements in radiotherapy have led to an . . . improved outlook, especially in intramedullary tumours' is unreferenced (the three references cited are for improved *surgical* techniques). Though refinements in radiation therapy technique may reduce 'late effects',[4] to which young children are particularly vulnerable,[2] we would like to know the evidence for this statement, which implies improved survival.

(5) The important role of radiotherapy in the palliative

management of spinal cord or cauda equina compression from recurrent primary or secondary malignancies was not discussed.

(6) The critical role of dexamethasone in emergency treatment was not mentioned.

(7) Chemotherapy now has a central role in the management of intraspinal malignancy,[5] yet receives no mention whatever. If a specific diagnosis can be made by biopsy (of the cord compressing lesion itself or of a separate site of tumour spread—for example, lymph node, bone marrow or, in the case of neuroblastoma, by a combination of biochemical and radiological criteria), laminectomy can be avoided. This is important because multisegment laminectomy can cause major morbidity. Besides the acute deterioration of neurological function, mentioned by Dr Cole, major cosmetic and functional consequences of laminectomy are also common. When radiotherapy and laminectomy are combined, these 'late effects' are particularly severe.[4]

(8) The role of 'lamina replacement' after laminectomy also deserves mention. The morbidity of the operation (especially in young children) will almost certainly be reduced by the general introduction of this technique.

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Dr Cole comments:

The authors have made some valuable comments on the *treatment* of spinal cord tumours, but they have failed to appreciate the aims of the annotation. My remit in bringing these rare, frequently misdiagnosed tumours to the attention of the general paediatrician, was to emphasise clinical features and diagnosis rather than treatment. Annotations by definition are brief and thus have to be selective. Perhaps Dr Pritchard and Mr Punt will agree that it is more important that paediatricians be aware of the pitfalls in the diagnosis of these conditions, rather than the details of their highly specialised treatment. Management of intraspinal neoplasms is of course varied and complex, demanding the multidisciplinary skills of the paediatric neurosurgeon, neurologist, radiotherapist, neuroradiologist, and oncologist (preferably in a UK CCSG centre). The onus of suspecting the diagnosis, however, falls squarely on the shoulders of the general paediatrician.

A more careful reading of my text will confirm that nowhere have I stated that space occupying lesions below L1–L2 cause spinal cord compression or that the peak incidence of neuroblastoma is in the newborn period (points 1 and 3). Point 4 is perhaps a little unfair, not only have Dr Pritchard and Mr Punt misinterpreted what was said, they have also quoted out of context. The references provided were apposite to the original text. Many radiotherapists would, I think, concur that developments in their field have led to improved quality of survival (that is, outlook) for patients with spinal cord tumours.[6–8]

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# The teenage coeliac

Sir,

We wish to comment on some defects in the study reported by Kumar *et al*[1] and to report our different findings.[2] The authors state that the height distribution of their patients was normal and unrelated to the strictness or otherwise of the gluten free diet, but we question this conclusion as they did not measure 32 of their 102 patients. They found that six of those measured (9%) remained below the third centile for height; if any of the 32 unmeasured had similar stature, the height distribution would clearly be below normal. Mean centile weights of those weighed were also below normal, so we find it difficult to accept that 'all patients were well and leading normal healthy lives' or that they 'remained well despite gluten ingestion' on the basis that they were regarded as asymptomatic, in view of the above findings and also that mucosal biopsies were taken only in 44 patients and 17 of these were grossly abnormal.

Our more comprehensive study showed a broad correlation between dietary compliance, height, weight, and mucosal state, serial height and weight being measured from mean age of diagnosis of 3·3 years to 10 years in 49 and 43 respectively of 52 patients. All patients regarded as complying well with the gluten free diet were of normal height and had normal or only slightly abnormal upper intestinal mucosa. Ten patients followed up from diagnosis at under 4 years to mean age 26 years, whose dietary compliance was poor from soon after diagnosis, were significantly shorter and lighter than normal and all had active enteropathy with appreciably lowered brush border enzymes. The mean heights and weights of those complying moderately were lower than those on good gluten free diets, but not significantly so.

We believe that if non-compliance with a gluten free diet starts in early childhood and persists, that adult stature will be reduced; at least three of the patients of Kumar *et al* probably fell into this category. We agree that gluten seems to harm the teenager less than in the young child and that a very few teenagers and young adults may seem to tolerate gluten for long periods. We also know that some patients don't realise that they are not completely well until they have experienced a considerable improvement in well being on a strict gluten free diet. Recent evidence suggests that complying with a gluten free diet reduces the risk of malignancy.[3]

In their final paragraph the authors are ambivalent about advocacy of a gluten free diet, although at one time they did advocate one. We would be gratified to learn that they accept that non-compliance with a gluten free diet would be harmful for most of their patients.

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Drs Kumar, Milla, and Professor Walker-Smith comment:

Thankyou for inviting us to reply to the letter of Colaco *et al.* None of us disagrees that a strict gluten free diet is mandatory in children and, indeed, this is the practice we all follow. There is also no doubt that shortness of stature can be due to untreated coeliac disease and, in our paper, three of the patients with their heights in the <3rd centile group in fact presented with this complication.

The point of our paper was to show that, despite being repeatedly advised to adhere to a strict gluten free diet, many teenagers did not follow this advice. Our clinics also have a dietician in attendance and the 'teenage' coeliac clinic has now been running for over 16 years with all patients being carefully monitored. The morphometric measurements of the jejunal mucosa, however, showed that many patients had abnormal mucosa despite stating that they were on a strict diet. It is well known that patients often say what they feel their doctor would like to hear!

To answer specific points: we reported measurements in only 70 of 102 patients as the remaining had been measured with less accurate techniques. The criticism put forward would also apply to their own paper where only 45 of 52 patients were reported—a far smaller number than in our paper. One explanation for the difference between our papers could be that although all our patients had reached puberty, perhaps some of the patients of Colaco *et al* had not as this point was not mentioned in their paper. Finally, if Colaco *et al* 'find it difficult to accept' that our patients were well 'despite gluten ingestion' we can only refer them to the references quoted in our paper or, indeed, to any clinician who sees patients with coeliac disease on a regular basis.

# IgG antibodies to Aspergillus fumigatus in cystic fibrosis

Sir,

We read with interest the report by Forsyth *et al* showing a significant negative correlation between the serum titre of IgG antibody to *Aspergillus fumigatus* and the Shwachman score and several indices of pulmonary function in cystic fibrosis.[1] The authors speculate that high antibody titre might lead to more severe disease through an increase in the amount of inflammation in the lung, though they acknowledge that conversely it might merely reflect colonisation of the damaged lung in those with more severe disease. Unfortunately they do not give details about *Pseudomonas aeruginosa* colonisation and specific *P aeruginosa* IgG serum antibodies in their patients.

We have recently done a similar study in 36 patients with cystic fibrosis aged 1–19 years. IgG ELISA to *A fumigatus* metabolic and somatic antigens was performed and the serum titre was obtained by comparing the results with reference serum. We found, as Forsyth *et al*, a significant negative correlation of the titre with forced expiratory volume in one second (r 0·61, $p<0·01$), forced vital capacity (r 0·59, $p<0·01$), peak flow (r 0·58, $p<0·01$), Shwachman score (r 0·55, $p<0·01$), forced expiratory flow measured between 25% and 75% of expired vital capacity (r 0·54, $p<0·01$), and a positive correlation with age (r 0·42, $p<0·01$). The closest association (figure) was, however, with the number of serum precipitins to *P aeruginosa* (determination kindly done by Dr Niels Høiby, Statens Seruminstitut, Copenhagen, Denmark) (r 0·79, $p<0·001$). Raised serum precipitins to *P aeruginosa* have previously been associated with advanced lung disease and chronic *P aeruginosa* bronchial infection in cystic fibrosis.[2] Any independent effect of

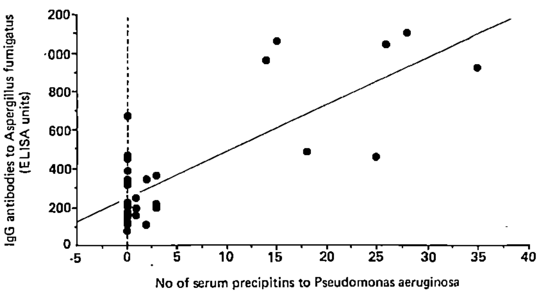

Figure *Correlation of serum titre of IgG antibodies to Aspergillus fumigatus and number of serum precipitins to Pseudomonas aeruginosa.* $y=24·328x+246·085$, $r=0·9$.

*A fumigatus* IgG antibody would thus be difficult to elucidate.

We think that raised IgG antibody to *A fumigatus* in cystic fibrosis is in most instances probably a secondary event in damaged lungs with chronic infection. There is a risk in some patients for the development of allergic bronchopulmonary asperigillisis (ABPA) which should be carefully investigated in every patient with cystic fibrosis. The role, if any, of IgG antibodies to *A fumigatus* in absence of ABPA remains to be established as Forsyth *et al* say.

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## Coarctation of the aorta corrected during the first month of life

Sir,

In their review of coarctation of the aorta presenting in the neonatal period, Ehrhardt and Walker emphasise the life threatening nature of this condition and the need for urgent referral to a hospital where confirmatory investigation and surgical correction can be performed.[1] They also point out that many babies arrive at their centre in poor condition and reiterate that initially an important clue to the diagnosis is the observation of a difference between blood pressure in the right arm and the lower limbs. No figure is suggested for the magnitude of this disparity but it is usually considered to be significant if greater than 20 mm Hg.[2]

Sphygmomanometric measurement of blood pressure in the newborn is not easy and many neonatal units have come to rely on electronic instruments which employ an oscillometric technique, such as the Dinamap (Critikon). The Dinamap, however, has been shown to overestimate blood pressure in some hypotensive infants,[3] and we have recently seen two normally grown term babies with coarctation in whom the Dinamap 8100 gave misleading results in the lower limbs. Both patients presented with heart failure and absent femoral pulses in the first week of life and despite the use of appropriately sized cuffs the blood pressure readings in the lower limbs were almost identical to the normal value obtained in the right arm. From our experience it appears that in cases of coarctation the Dinamap can overestimate blood pressure in the hypotensive lower limb and thereby obscure the underlying diagnosis. If absent femoral pulses suggest coarctation but the Dinamap shows no significant difference between upper and lower limb blood pressure, urgent referral to a cardiothoracic surgical centre should not be delayed.

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## Accidental feeding of a dilute antiseptic solution to five babies

Sir,

Five normal newborn breast fed babies were accidentally fed a dilute antiseptic solution (chlorhexidine 0·05% with cetrimide 1%) in place of sterile water and developed caustic burns of the lips, mouth, and tongue within minutes; one baby became quite severely ill due to acute pulmonary oedema, but all survived without sequelae.

A full account of this incident in 1976 has been published elsewhere,[1] but I would like to draw it to the attention of a wider paediatric readership. Babies at this hospital are routinely given 'top ups' of sterile water if necessary after feeding from the breast so as to allèviate thirst but not so as to give a feeling of satiety—thus encouraging them to feed from their mothers; this avoids the pitfalls of giving top ups of cows' milk formula or glucose solution.

The five babies developed symptoms almost simultaneously, and a rapid inspection of the Milk Room showed that, in addition to sterile water, glucose solution, and proprietary milk feeds, there were a number of full and empty clear 50 ml bottles of a dilute antiseptic solution of chlorhexidine 0·05% with cetrimide 1%. This was normally supplied in 500 ml fluted opaque glass bottles, which were temporarily unavailable, so the suspicion was that the antiseptic solution had been given as a top up feed.

It is likely that the babies' symptoms were mainly due to the caustic action of cetrimide 1%[2 3]; fortunately contact with the mixture was necessarily very brief as it is irritant with an unpleasant taste leading to immediate attempts to spit it out. Treatment should consist of avoiding gastric lavage; whole egg mixed in milk can be given to neutralise chlorhexidine, but there is no specific antidote to cetrimide. Four affected babies were given hydrocortisone and ampicillin sodium intramuscularly, and two who were irritable were given intramuscular phenobarbitone.

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## Mildly anaemic toddlers respond to iron

Sir,

Some general readers might be tempted to conclude from the paper by Parks *et al* that, after oral iron treatment, a change in mean haemoglobin concentration from 108 g/l to 126 g/l, mean corpuscular volume from 64·8 fl to 69·3 fl, and mean serum ferritin from 8·3 μg/l to 14·8 μg/l constitutes 'iron deficiency, end of haematological story'.[1] This will of course be far from the case in some Asian toddlers.

Haemaglobin A2 and F determination will not exclude α thalassaemia, which occurs with high frequency in Asian populations. A mean corpuscular volume of 69·3 fl is below the 3rd centile quoted by Dallman and Siimes,[2] whose reference group 'may well include iron deficient children' as Parks *et al* point out themselves. From the data they present, some of the children could well have α thalassaemia, which can coexist with iron deficiency. At the very least their families could be investigated. What diagnoses did they make in those whose mean corpuscular volume remained substantially lower than the mean of 69·3 fl (the SD was 3·9 fl) after iron treatment?

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## Effect of misoprostol on fat malabsorption in cystic fibrosis

Sir,

The improved fat malabsorption shown in the patients with cystic fibrosis reported by Robinson *et al* is interesting and significant but the data presented are inadequate to make a judgment as to the drug's place in patient management.[1] A study of this type should include the number of pancreatin (Pancrease, Ortho-Cilag) capsules taken by the patients. The fact that only three patients achieved better than 85% absorption and six suffered from 'chronic abdominal pain' suggests that their malabsorption was inadequately controlled due to inadequate dosing with Pancrease; perhaps an increase in Pancrease would have been more appropriate than the addition of misoprostol, yet another medication for their already overloaded treatment regime.

If the absolute values of intake, output, and enzyme dose are not included it is impossible to confirm that these patients were receiving too small a dose of enzymes to control their malabsorption at the start of the study as appears to be the case.

It would be unfortunate if physicians responsible for patients with cystic fibrosis were to add misoprostol rather than treating their patients' malabsorption correctly—that is, increasing the dose of modern pancreatic microsphere preparation until symptoms are controlled, then checking the faecal fat output and intake. If the fat absorption is less than 90% the dose of enzyme should be increased and the process repeated. The manufacturer's literature is misleading as many patients require 6–10 capsules per meal of the microsphere preparations available in the United Kingdom. It would then be of interest to know if the addition of misoprostol to the treatment of patients with cystic fibrosis having optimal control of their malabsorption by conventional preparations would further improve their fat absorption.

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Drs Robinson, Sly, and Smith comment:

We thank Drs Littlewood and Kelleher for their comments but it would appear that they have missed the main point of our paper, and as such our suggested role for misoprostol in the care of patients with cystic fibrosis. The idea that a patient with cystic fibrosis who does not have normal fat absorption on enzyme supplements, will always achieve normal absorption by simply increasing the enzyme quantity until this normal value is reached is wrong. As mentioned in our paper it is now well recognised that malabsorption in cystic fibrosis is not simply a matter of exocrine pancreatic insufficiency but that other factors such as gastric acid hypersecretion, small bowel mucosal abnormalities, and biliary abnormalities may all play a part in the malabsorption in cystic fibrosis. None of these factors would be improved by simply increasing the number of enzymes administered. Thus the presence of abdominal pain or residual malabsorption on enzyme treatment does not necessarily reflect inadequate oral doses of enzymes—rather it may reflect either inefficient functioning of orally administered enzymes or the presence of non-pancreatic factors which themselves are producing malabsorption. As such, the finding of residual malabsorption in a patient on high doses of enzymes should not institute a 'knee jerk' reaction to increase the enzyme quantity.

The patients enrolled in this trial were all receiving high dose enzyme treatment (mean daily capsule intake 35 capsules, range 26–70). This corresponds to the dosage range as suggested adequate by Drs Littlewood and Kelleher. We are currently studying whether the addition of even further enzymes above this range produces further increases in absorption and our subsequent publications will address this topic. The fact that those patients who had >10% malabsorption on their enzyme supplementation achieved a significant decrease in malabsorption on misoprostol suggests that factors other than lack of enzymes were contributing to their residual malabsorption. To prevent acid destruction of enzymes they are prepared with an enteric coating which permits their release only after contact with an environmental pH above 5·8. Misoprostol improves fat absorption by raising the pH of the small intestine, thus permitting greater release of the enzymes by exposing them to a higher pH for a longer time, and also preventing their destruction by an acid environment. Adding more enzymes into a hostile environment is unlikely to improve fat absorption. Under these circumstances the more rational approach to treatment is to optimise the environment for efficient functioning of the enzymes. We would suggest that the addition of two further tablets a day, which improve the efficiency of a patient's current enzymes, is less of a strain to the patients 'already overloaded treatment regime' as described by Drs Littlewood and Kelleher than the addition of further inefficient pancreatic enzymes.

We do not suggest that misoprostol has a role in replacing rational doses of enzymes, rather we would suggest that the days where residual malabsorption in those patients already on high dose enzymes is treated simply by a further increase in enzyme therapy have now passed and a more logical and widespread approach to malabsorption should now be employed.

The improvement in absorption achieved by a standard dose of enzymes is widely variable from patient to patient and simply studying intake and output values does not prove whether sufficient enzymes have been administered as is suggested by Drs Littlewood and Kellher. Rather, analysis of these values gives an indication as to the efficiency of enzyme function. Again, the idea that residual malabsorption on a high enzyme intake implies insufficient enzyme supplements is, we feel, incorrect and an over simplification of the area of fat malabsorption in cystic fibrosis.

**Reference**

[1] Robinson PJ, Sly PD, Smith AL. Effect of misoprostol on fat absorption in cystic fibrosis. *Arch Dis Child* 1988;**63**:1081–2.

*Archives of Disease in Childhood,* 1989, **64,** 1098–1100

# Book reviews

**Paediatric Problems in General Practice.** By M Modell and R Boyd. 2nd ed. Pp 318: £15 hardback. Oxford Medical Publications, 1988. 0–19–261736–2.

The British Paediatric Association should issue this book with a health warning aimed at consultant paediatricians 'This book could seriously deprive you of work—not the work that you should be doing but the work of unnecessary referrals to paediatric outpatients by general practitioners'.

A general practitioner who has read this book, and indeed a paediatric senior house officer or registrar, would have found a treasure trove of the sort of good solid basic paediatrics that I know I need to practice effectively as a general practitioner. Not having read the first edition I was thrilled to find a paediatric book apparently purged of eponymous conditions and the dreaded glycogen storage diseases. Here was a paediatric text book, although it can hardly be called that, that actually stimulated me and kept me awake rather than put me to sleep.

This is really a book for the majority of doctors in the country who treat children—that is, general practitioners. This is not to be patronising. The book is no less well written and well researched and up to date for that, in fact more so. I think the best description would be that it is a finely tuned book. It is well structured, well bibliographed, and clearly and attractively set out. I particularly enjoyed the widely interspersed illustrative case histories, which in my experience are frequently the hallmark of a good medical read. The layout is problem orientated rather than system orientated and to this extent it matches the children who consult us.

Among the problems that this book addresses are those of ethnic minorities and the authors are not afraid to discuss the doctor's attitudes as well as his medical knowledge.

Naturally the book covers the controversial area of sexual abuse and non-accidental injury, although I found that to some extent there was a weakness in the sexual abuse advice in as much as that there was an admirable amount of explanation of how to diagnose sexual abuse but very little guidance on how to deal with disclosure and very little indication of the sort of work that had to be done with the family in the period after diagnosis.

On a more general approach to child psychiatric problems, however, there is an excellent account of how to proceed with a child psychiatric referral and good advice on dealing with divorce and bereavement.

The section on prevention was comprehensive but there seemed to be very little real feel for the use of computers in general practice paediatrics. Perhaps this could be a task for the third edition.

Time after time while reading this book I have tested it against my needs as a clinician meeting problems that my children patients present to me daily—growth, painful joints, recurrent abdominal pain, headache, urinary tract infection and, of course, asthma—plus many others that I am sure any other general practitioner can mention. Every time the book scored full marks for common sense, practical suggestions, and up to date management.

In a review all I can do is recommend a book and in this case to general practitioners and training grade paediatricians—I wish I could do more—I wish I could send a copy to everyone of them.

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**The Very Immature Infant: Less than 28 weeks' gestation.** Edited by A Whitelaw and RWI Cooke. Pp 1157: £28·25 hardback. Churchill Livingstone, 1988. ISBN 0 443 04040 0.

All paediatricians who look after preterm infants will find items of interest in *The Very Immature Infant* in which the editors, Andrew Whitelaw and Richard Cooke have compiled a series of short review articles on topics relating to infants less than 28 weeks' gestation. Whereas many such reviews are published in North America, all the authors in this book are British and they provide a different perspective on many issues and also useful epidemiological and other data relating to this country.

The different authors cover specific areas in which they have contributed to our understanding. These include a useful review on the physiology of the mid trimester fetus by Rodeck and Nicolini; new non-invasive methods of assessing brain oxygenation and haemodynamics is described by Reynolds *et al*; there is a chapter on the neurophysiological assessment o immature central nervous system by Eyre and a particularly helpful chapter on the immature visual system by Fielder *et al.* Many of the articles described the considerable advances in our knowledge and understanding of these very immature infants but our ignorance about other areas is also readily apparent. As the book covers only a number of selected topics several important areas, such as infection and periventricular haemorrhage, have been omitted.

The editors have concentrated on the biology of these very immature infants. There is only an extremely brief chapter examining clinical management (b McIntosh) and a single chapter on bot outcome and costs (by Cooke). The brevity of these articles precludes consideration of difficult but crucial ethical questions surrounding the care of the immature infant such as how to decide on whether or not an infant is too immature to warrant active resuscitation and how best the increasing demand for care of such tiny infants can be met. With the impending reorganisation of the National Health Service it is likely tha these are issues which paediatricians will shortly need to address and it is unfortunate that more space was not devoted to them.

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**Fetal Neurology.** Edited by A Hill and J Volpe. Pp 317: $86·50 hardback. Raven Press, 1989. ISBN 0–88167–469–9.

Subspecialisation evolves: first there was fetomaternal medicine, then fetal medicine, and now fetal neurology. Advances in ultrasound have allowed study of the neurodevelopment of the fetus and form the basis for all the subjects covered in this

The lasting impression, however, is v little we know at present about the rs controlling, modifying, or altering development in utero. The majority work reviewed is at a research stage its clinical relevance is unclear or tain.

e 13 chapters are divided up into three ns—antepartum fetal assessment, partum fetal assessment, and major fic fetal conditions. Because much of resentations are controversial and the r(s) may have a biased viewpoint the ice of editorial commentary on each er is valuable and puts the subject perspective, though they could have more critical.

major criticism is the excessive ntration on fetal hypoxia. Six chapters concerned with this subject in one t or another (and contained informa- that has been regularly reviewed in books and journals) and yet only one er dealt with fetal behaviour.

other clear message from the book is fetal neurobehavioural development nly be properly understood when the ations of various fetal neurological neters are related to developmental me in infancy and childhood.

nay well be that the second edition of ook will be of more widespread l relevance and interest.

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**Development of Mature Walking.** By therland, R Olshen, E Biden, and att. Pp 227: £24 hardback. Blackwell tific Publications/MacKeith Press, ISBN 0–632–01902–6.

ticated study of the gait of 309 al children in 10 age groups from ars makes a formidable story. Alto- r 449 recordings were made on the teered subjects, over 90% of whom white. The data and graphics presented well become the basis for a future rt' system for gait analysis in children. would be a 'black box' capable of ting, processing, and interpreting the on which clinical decisions can be Though the San Diego laboratory is the most advanced in the world, computer has had to deal with so data that the turnaround time has been a problem. That will speed up. The difficult part will be programming the interpretation which depends on evidence for effective treatment of particular abnormalities of motion, electromyography, and force.

Some clinicians may find that the book offers more than they want to know about gait. There are 87 figures, 13 tables, and five pages of recording charts. One figure includes 24 graphs. In the middle of the book there are 80 pages of continuous figures. The complexity of the data is illustrated by the six pages explaining their mathematical treatment. The formulae underlying their 'bootstrap' technique are beyond the comprehension of a reviewer more familiar with shoestring methods.

Their anthropometric data are easily assimilated and helpful. The gait analysis system used four motion picture cameras, a force plate, and electromyography linked to a minicomputer. As a scientific study this monograph is a landmark. Departments of bioengineering, gait laboratories, physiotherapy teaching schools, and academic departments of orthopaedic surgery and paediatric neurology will find it a classic source of reference. If the next 10 years bring the data justifying its cost effectiveness, this approach will have been vindicated.

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**A Colour Atlas of Muscle Disorders in Childhood.** By V Dubowitz. Pp 182: £40 hardback. Wolfe Medical, 1988. ISBN 0–7234–0811–4.

This is not so much a textbook more a glossary of cases from Victor Dubowitz's wide clinical experience. However, I suspect that there are many other paediatricians who like myself find the good presentation of a clinical case, demonstrating the features of a particular condition, a far more meaningful way to learn than a dry description of the condition itself.

The book, well titled as an atlas, covers all the major muscle disorders of childhood, the common and the uncommon, in its 182 pages, 80% of which are pictures. The layout is excellent. Each section starts with a short summary of the disease in note form in blue, easy to locate, tables. The summary covers definitions, age of onset, presenting symptoms, clinical signs, and associated features. The usual course and prognosis is described. Investigations, biopsy findings, genetics, and principles of management are outlined. These summaries provide a quick *aide memoire*, which will be useful for those studying for postgraduate examinations and those involved in teaching.

The case histories themselves are succinct and useful in that many describe the 'not-so-typical' presentations common in everyday practice, the multitude of children depicted in the super clinical photographs reflecting the wealth of experience of the author. There are good illustrations of surgical appliances—braces, calipers, etc—which would be helpful for parents to see—all the children are smiling! The well reproduced biopsy pictures are well integrated into the text and therefore much more digestible than a separate section just on biopsy appearances.

The section on investigations only describes needle muscle biopsy. The section on ultrasound is limited to only a short description. I would have preferred more detail with more photographs of ultrasound appearances of common disorders as this is an area unfamiliar to many paediatricians. The bibliography consists of only 10 references; a more comprehensive one would have been helpful.

The Atlas will appeal to general paediatricians as well as those with an interest in neurology and also to community paediatricians with responsibility for disabled children. It will also be of interest to other disciplines working with such children.

When this book arrived I immediately found myself searching through it for a description of the condition the name of which I had just seen that day for the first time on the biopsy result of a little patient of mine—I was not to be disappointed!

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**Pregnancy and Risk.** By D James and G Stirrat. Pp 209: £18 paperback. Wiley, 1988. ISBN 0 471 91188 7.

Media and public obsession with the minutiae of medical wizardry, coupled with the occasional or frequent medical success in a seemingly hopeless situation, has reinforced the myth of human immortality. This is most marked during the perinatal period, where the possibility of an outcome other than happy is dismissed or subjugated. This tome discusses in a dispassionate and well argued fashion the risks attached to successful procreation.

Medical audit presently enjoys a profile as high as that of the environment on the political agenda and we are introduced to the necessary concepts in a lucid and understandable form, despite considerable statistical content. Thereafter, the various stages of procreation are discussed in a temporal progression until medical audit is discussed from a practical viewpoint as the final offering. Clinical geneticists are still a rare breed, the genetics chapter is well written and contains sufficient data for clinicians to embark on genetic counselling with substantiated facts easily accessible.

Condensing a large topic into a handbook renders the authors open to sins of commission as well as omission.

Two chapters: 'Risk at the booking visit' and 'Risk and the neonate' were uncomfortable—couldn't decide whether to be a textbook or not and included considerable but incomplete data—which leaves the reader insecure at taking advice from these chapters. The list of prescribing in pregnancy is incomplete, so loses authority and becomes useless as a basis for prescribing.

The chapter on labour separates overall risks into component parts, which affords a worthwhile basis for targetting resources in attempts to reduce mortality in areas where this is feasible. Interestingly the reference discussing neonatal intensive care and mental retardation is far later than the seminal work of Brimblecombe *et al* from Exeter. Apgar scores and cardiotocographs, forming part of the obstetric/paediatric interface, have their merits and demerits well ventilated. The controversy of caesarean section and preterm labour, however, is dismissed with references, while prolonged labour is blessed with a largely historical treatise. The problems of the neonate are potentially legion and the salient areas should be chosen with care. Inclusion of simplistic and somewhat worthless information is an ill afforded luxury in this book and the chapter failed to impress.

The book attempts, mostly successfully, to encompass the multifaceted problem of pregnancy and will be useful to obstetrician and paediatrician alike. It is easily read, enjoyable, but factual without tedium or verbosity.

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**Edmond Went Far Away.** By Martin Bax, illustrated by Michael Foreman. Pp 40: £8·95 hardback. Walker Books, 1988. ISBN 0–7445–1060–0.

The perfect bedtime story is one that keeps parents awake and sends children to sleep. This story is written by a paediatrician and is about Edmond who lives in a farm house. He says goodbye to all his animal friends and goes on a long walk. First he goes through a copse patting the trees goodbye, then down a muddy path, and finally he climbs up a long hill. This took him a long time and on the way he imagines that all his animal friends are with him.

When he got to the top of the hill he looked down at the new world on the other side and began to panic slightly because he wasn't sure whether to go home or not. A familiar figure caught his eye and he was pleased to see that it was his father who had followed him. They explored the new world together, rowing round a lake, building a fire of driftwood, eating baked beans, and spending the night in sleeping bags. The next day when Edmond returned home from his adventure his animal friends were very pleased to see him and I suppose his mother was too.

When I first looked at the book the part that stood out most were the wonderful illustrations which made the story come to life. Although they weren't greatly detailed they were colourful and very effective. This is an ideal bedtime story book, read by either parents or children. It is suitable for 5–7 year olds, although younger ones might have difficulty with some of the words. The good thing is that there is no moral to the story. Children don't want morals at bedtime and this story is far more en without one.

Lindsey

# *Video review*

**Screening and Surveillance for H Impairment in Young Children.** N ham Health Authority, 1987. Video ing Package, £98·50.

The detection of hearing impairm young children over the country as a is poorly carried out, and this is conf by the late ages of diagnosis of many deaf children. This screening packag excellent aid for local authorities wh trying to improve the outcome of screening programmes and will be a supplement to pre-existing training

The package consists of two pa trainers' manual that sets out the es activities that have to be taught o programme and the recommended ti the training modules, including a full practical training. The second part package is the video, which illus clearly the points raised in the tr manual and is excellent teaching m although insufficient for use on it The video and manual cover all asp the distraction test, including problems, in a concise manner an recommendations are followed I a that there will be a marked improve the detection of hearing loss.

There are some sections that nee expanded but this can be carried out trainer during the various activity se The manual stresses the fact th trainer should be appropriately train experienced in hearing screening ques and this needs to be empha local authorities are to implemen training package. Given this prereq however, I would highly recommend an aid to training health visitors and professionals involved in screenin dren's hearing.

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